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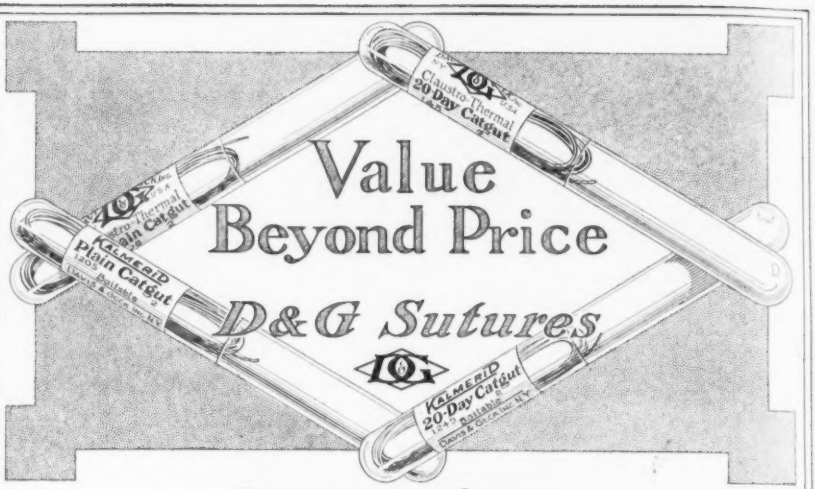

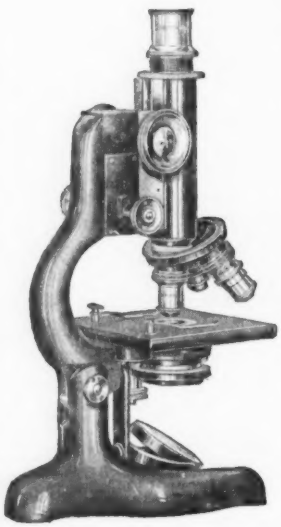

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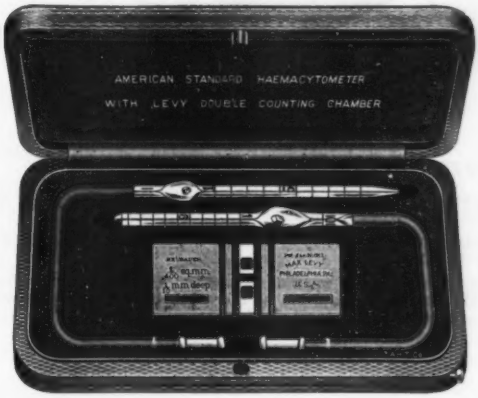

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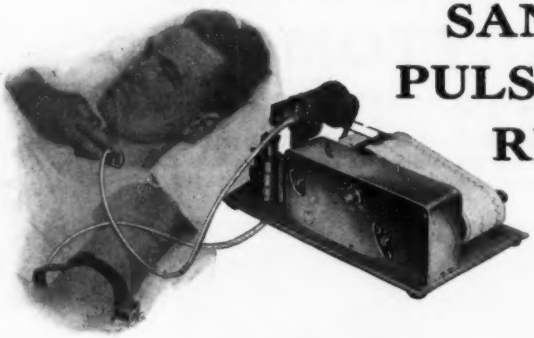

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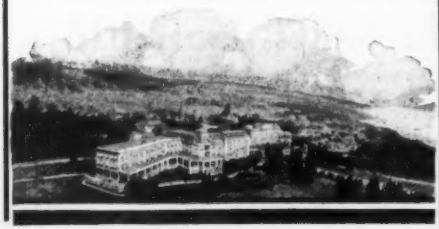

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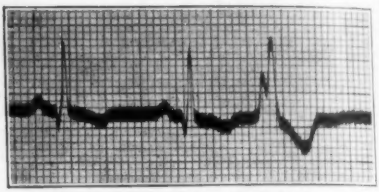

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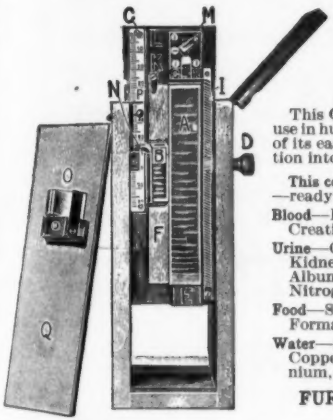

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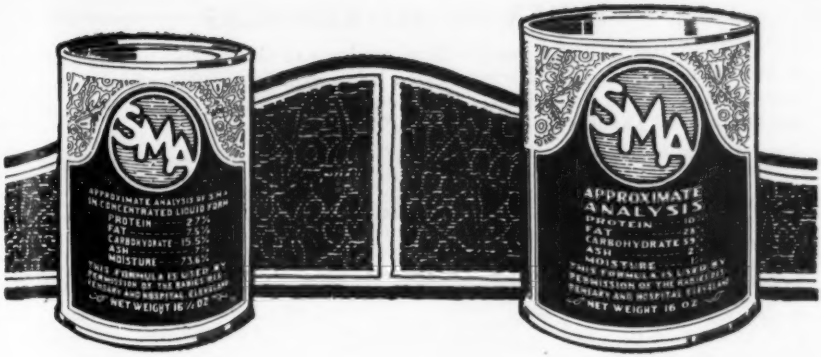

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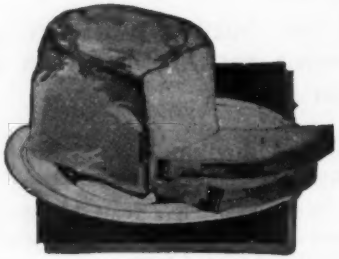

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OF THE MEDICAL SCIENCES

AUGUST, 1922

ORIGINAL ARTICLES.

THE ACTION OF DIGITALIS IN CASE OF AURICULAR FIBRILLATION AND FLUTTER.*

THIRD LECTURE

By Thomas Lewis,

UNIVERSITY COLLEGE HOSPITAL, LONDON, ENGLAND.

The original observations upon which this lecture is largely based have been carried out by my collaborators and myself during the past twelve months to determine if the reaction of auricular fibrillation and auricular flutter to therapeutic doses of digitalis may be explained by the theory that these two disorders of heart rhythm are essentially due to circus movement.† First we will consider the action of digitalis upon the rate of the ventricle, and later we will consider the main problem of its action on the auricle. As will appear, knowledge of the first is relevant when we explore the second problem.

The Nature of Digitalis Block. The question as to how digitalis produces heart-block, the universally recognized cause of ventricular slowing in cases of auricular fibrillation, is one upon which a conflict of opinion exists. The evidence is not of so simple a character as it was once thought to be. The discussion is rendered

* Based on observations carried out on behalf of the British Medical Research Council. The Nathan Lewis Hatfield Lecture, delivered before the College of Physicians of Philadelphia, May 5, 1922.

† Especially associated with me in the most recent observations have been Dr. A. M. Wedd, of Pittsburgh, and Dr. C. C. Iliescu, of Bucharest; we have also received much assistance from Dr. A. N. Drury, who has for some years worked actively upon closely allied problems.

of more consequence because precisely similar problems arise in the case of ventricular slowings other than those due to digitalis and in other forms of slow ventricular action. The argument turns, as we shall presently see, mainly upon the reaction of the ventricle to atropine.

We start with the simple and uncontested fact that digitalis produces ventricular slowing in cases of auricular fibrillation; and we conclude from evidence in our possession that this retardation is due to block at the *A-V* junction.[8] Experiment teaches us that *A-V* block may be produced by digitalis in one of two ways, by increasing the tone of the vagus (an indirect effect exerted upon the junctional tissues) or by a direct action on the junctional muscle.[3, 11, 16] The action, whether direct or indirect is exerted, according with, the indications of recent experiment, upon that portion of the junctional tissues termed the *A-V* node.[11] The direct and indirect action each has the same end-effect; each produces a condition at the *A-V* node rendering it less capable of conveying impulses. The immediate effects upon the tissue are not quite the same; in the case of the nerve effect, we have to deal apparently with a reduced rate of recovery of the tissue; in the case of the direct action we have to deal apparently with a prolongation of systole, whereby the time allowed for subsequent recovery is reduced. Be that as it may the end-effects are both declared as lesser or greater degrees of block. Block at the *A-V* junction is the only known means by which digitalis can influence the rate at which the ventricle will respond to an auricle in a constant and unaltered state of fibrillation. Is this block produced by a direct action or by an indirect action through the vagus in clinical fibrillation? The problem would appear easy to solve. Digitalis slowing is produced in a case of fibrillation and the patient is then atropinized. The atropine paralyzes the vagus and the ventricular rate returns to about its former level. What more natural than to conclude that digitalis exerts its action through the vagus. That is the conclusion to which Mackenzie came,[12] when he first used atropine for this purpose. But, as Cushny[4] has very properly pointed out, the problem does not end here. Cushny's argument is one of some intricacy and has not been understood widely and clearly. It may be illustrated diagrammatically (Fig. 1). Let us suppose that the line *cc* represents the level at which the ventricle beats in response to a fibrillating auricle when the patient is uninfluenced by drugs; and let us further suppose that this rate is reduced from *c* to *e* under the influence of digitalis given in therapeutic doses. Atropine is now given, and the rate returns, let us say, from *e* to *c*. The fall which digitalis produced is completely wiped out by the action of the atropine. Yet we are not justified in concluding that the digitalis fall of rate from *c* to *e* is vagal in origin. As Cushny has shown, if an

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initial dose of atropine is given in the predigitalis stage, the rate is lifted temporarily to *a*. In other words, the original level *c* was maintained at a comparatively low point by normal reflex vagal tone; and when this level is further reduced (to *e*) by digitalis, the subsequent rise produced by atropine may be attributed to one of two effects: (1) To the abolition of the original reflex vagal tone prevailing at level *c* and still maintained after digitalization, or (2) to the abolition of a digitalis vagal tone.

To obtain *proof* that the fall on digitalis is due entirely to an increase of preëxisting vagal tone, one view which has been held of the action of digitalis, it would be necessary to show that atropine can raise the rate of the digitalized heart from level *e* to level *a;* for atropine, given in a sufficient dose to completely paralyze the

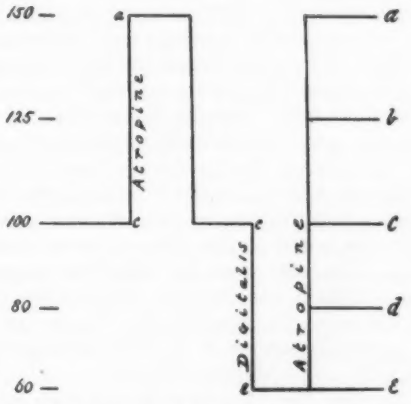

FIG. 1.—A diagram of the reaction of the ventricle, in auricular fibrillation, to digitalis and atropine. The diagram illustrates the text description.

vagus, should abolish, not only the original reflex vagal tone, but also that portion of the final vagal tone which has been superadded by the digitalis. The view may be held justifiably that the rise from *e* to *c* under atropine, is due, as was the original rise from *c* to *a*, to the abolition of normal reflex vagal tone and that the fall from *c* to *e* under digitalis was in reality the effect of a direct action which has been uninfluenced by the second dose of atropine. The level (*c*) at which the ventricular rate stands after digitalis and atropine is far below the level (*a*) at which it stands under atropine alone, and this should not be the case, providing that the digitalis fall is purely vagal, and if a dose adequate to abolish all vagal action is given on each occasion. Thus, it is evident that the final rise under atropine from *e* to *c* cannot be used as proof that the action of digitalis is vagal.

On the other hand it cannot be used as proof that the action is purely a direct one, the second view of digitalis action which has been held. *Proof* of a purely direct action would be obtained only if the second and adequate dose of atropine failed to produce a rise, namely, if the level remained stationary at *e*. It may be argued that since the rise from *e* to *c* is no greater than the rise from *c* to *a*, this relation constitutes evidence that both these rises are due simply to the abolition of the original reflex vagal tone, and that digitalis vagal tone plays no part in the fall *c* to *e*. This argument is only valid if a certain measure of vagal tone produces equal falls of ventricular rate from different initial levels and if we can be sure that when the ventricle slows under digitalis *the original measure of reflex vagal tone is maintained;* but the first assumption is scarcely justified, since a halving of ventricular rate is produced more easily when the rate of the ventricle is initially high than when it is low, and a halving of rate at a high level means a much larger fall in the number of beats per minute than does halving at a lower rate. In respect of the second assumption it may be argued that, when the heart slows under digitalis, the natural reflex vagal tone would tend to pass into abeyance and might vanish entirely.

We are left therefore in this position. Proof of uncomplicated vagal action requires a lift of rate from *e* to *a*. Proof of uncomplicated direct action requires maintenance of the level at *e*.

Now, neither one nor the other form of curve characterizes the actual reaction. The rate does rise when an adequate dose of atropine is given, but it rises to very different levels in different patients. In the series described by Mackenzie and by Cushny, the rise was generally either to a level intermediate between *e* and *c* or actually, as in Mackenzie's case, to *c*. It will be clear that the less the rise, the more is a direct action evidenced; the greater the rise, the more is vagal action evidenced; but that, so long as there is a rise, but a rise which fails to reach level *a*, *proof* of an uncomplicated action, direct or indirect, is not forthcoming.

The Dose of Atropine. The assumption that the dose of atropine given is adequate completely to paralyze the vagus is one of such consequence to the argument that it needs to be explored in some detail.

Actually the dose required to paralyze the human vagus has not been ascertained either for normal subjects or for cases of fibrillation, digitalized or undigitalized. The general assumption appears to be that one-fiftieth of a grain of the sulphate given hypodermically is sufficient.

This assumption appears to be based in part upon the belief that atropine has an "all or nothing" action; that if the ventricle is released at all, it is fully released. The last belief is not well founded. If atropine is injected intravenously repeatedly and in minute doses into dogs, it is not difficult to show that the drug first abolishes

the effects of weak vagal stimulation, and that further doses are required before the effect of strong vagal stimulation disappears. In dogs weighing 10 kgs. a dose of 0.2 to 0.4 mg. of atropine will abolish the effects of weak stimulation; in the same dogs doses of 0.4 to 1.0 mg. are required to abolish the effects of strong stimulation. The dose required to produce complete paralysis is approximately 0.05 to 0.1 mg. of atropine per kilo body weight. Calculated on the same bases for a human subject of 75 kilo weight, the dose required would be 3.7 to 7.5 mg. (or approximately one-seventeeth to one-ninth of a grain). From this calculation it might be anticipated that one-fiftieth of a grain given to the human subject would on direct tests prove to be inadequate. At the same time it should be noted that while in dogs doses of from 0.2 to 0.4 mg. will not abolish all reaction, yet they very notably reduce the reaction to strong stimulation of the nerve. Thus, it is to be inferred that since one-fiftieth of a grain given to a patient is sufficient to produce a conspicuous rise of ventricular rate, a large subsequent rise of rate on completely saturating the vagus with atropine is not to be expected.

Clinical Observations. With few exceptions the dose given in published cases has been one-fiftieth of a grain of atropine sulphate administered hypodermically. In one of Cushny's cases one-fiftieth of a grain was administered on one occasion and one-twenty-fifth of a grain on a second occasion, the ventricular rate rising to approximately the same level on the two occasions.[4] It has been felt that this single observation, from which it is argued that one-fiftieth of a grain is an adequate dose, constitutes insufficient evidence; in a preliminary series of observations upon three cases of auricular fibrillation, we gave separately and at suitable intervals doses of one-twentieth and one-tenth of a grain with a view to comparing the resultant ventricular curves. In two cases no difference was apparent; in the third case the rise with the one-tenth of a grain was appreciably the higher. In a second series of observations upon similar cases we have given one-fiftieth of a grain of atropine hypodermically, and have followed this by a further and intravenous injection at the height of the reaction to the first dose. The results are variable. In some few patients one-fiftieth of a grain given hypodermically appears to be adequate. More frequently, however, the rate rises further on the second dose (Figs. 2 and 3). The second rise amounts to as much as 10, 15 or 20 beats per minute. Through and through this added rise seems to be greater in patients who have previously been brought under the influence of digitalis. That is to be expected if we take the view that a dose adequate to cut out normal reflex vagal tone is not necessarily adequate to abolish this tone and also that which we might suppose added during the period of digitalis slowing.

Thus it would appear that the doses used to test the measure

of vagal tone in both the digitalized and undigitalized case have not always been adequate. The curves published by Mackenzie

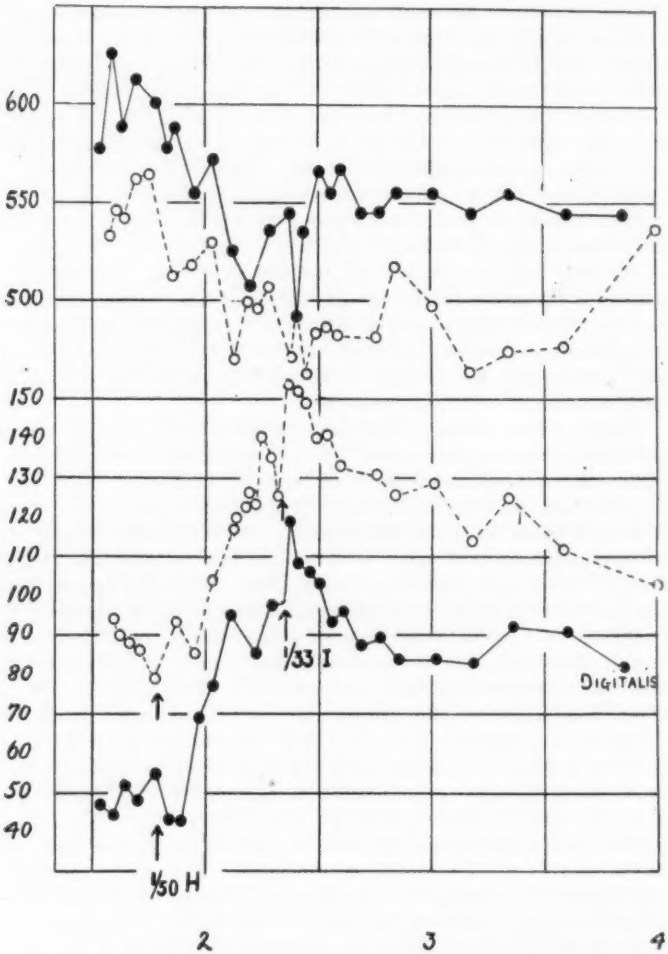

FIG. 2.—A chart of the auricular (upper curves) and ventricular rates (lower curves) in a case of fibrillation of the auricles. The curves were constructed from the patient while digitalis free (plain circles) and while under digitalis (black circles) 7½ drams of tincture had been taken in eight days. In both circumstances a hypodermic dose of $\frac{1}{30}$ of a grain of atropine was followed by an intravenous dose of $\frac{1}{33}$ of a grain.

and Cushny to illustrate the effects of abolishing vagal tone in digitalized patients cannot be regarded as wholly representative.

When fuller doses, single doses of one-tenth or of one-twentieth of a grain, or two doses bringing the total to one-twentieth of a grain, are administered, the rise is almost always above the level of the predigitalized rate (level *c*); often it is considerably above this

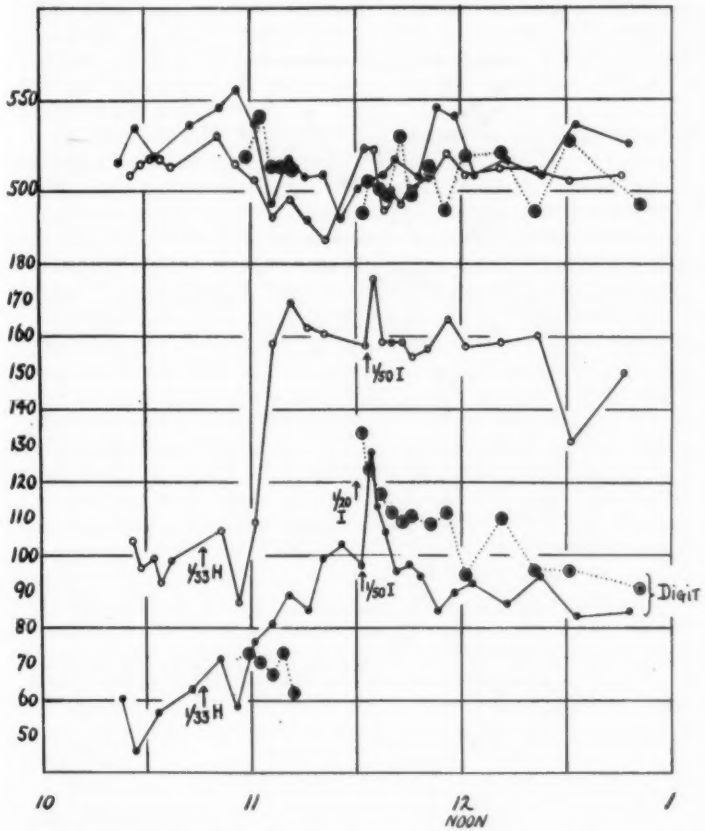

FIG. 3.—A similar chart from a second patient, to which has been added the curve produced by a single intravenous dose of $\frac{1}{10}$ of a grain of atropine (double circles) while the patient was still under digitalis. The hypodermic injections in the case of the first curves were $\frac{1}{33}$ of a grain and the intravenous doses were $\frac{1}{50}$ of a grain. 9½ drams of tincture of digitalis had been taken in eleven days.

rate and exceptionally it may approach very closely to the rate obtained by the similar administration of atropine in the predigitalis stage (level *a*). Of the two procedures the former appears to be the more effective (Fig. 3), and presumably this is so, because when a hypodermic dose is given the reaction is not usually at its height for

twenty minutes, while if a similar intravenous dose is given, recovery usually begins before this time has elasped. It is to be concluded therefore that the full effect of one-fiftieth of a grain is not always shown when the drug is given hypodermically. In one patient (Fig. 4) the original rate was 101, and atropine (one-twentieth of a grain) drove the rate to 232. The patient was now given full

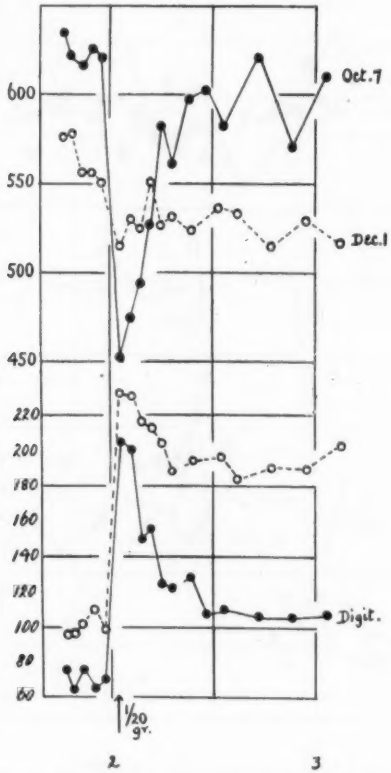

FIG. 4.—The effects of injecting $\frac{1}{20}$ of a grain of atropine intravenously in a case of auricular fibrillation, before (plain circles) and after (black circles) bringing the heart under the influence of digitalis (9 drams of tincture in twelve days).

therapeutic doses of digitalis and the rate fell to 70; a dose of one-twentieth of a grain now increased the rate to 205. The first atropine rise was of 131 beats, the second of 135 beats. It is to be observed that the full rate of 232 was not attained at the second injection, consequently it cannot be concluded finally that the digitalis slowing in this case was of purely vagal origin; but it

can be concluded with some approach to finality that in this case the digitalis slowing was in large part vagal in origin, for the second dose of atropine almost abolished, not only the fall on digitalis but also the preëxisting reflex tone. The differences before and after the administration of digitalis was one of 31 beats per minute; the difference in the maximal rates attained under atropine was 27 beats. These two differences cannot reasonably be regarded as equivalent; the first, occurring while rates of 200 or over prevailed, is a minor difference as compared with that obtained at rates of 100 and under.

In view of such observations it seems reasonable to conclude that in some cases of auricular fibrillation, digitalis does exert an influence through the vagus and that in greater or lesser measure this increase of vagal tone is responsible for the ventricular slowing. It still cannot be concluded that in any patient, the fall of rate is wholly vagal; neither can it be said that an increased vagal tone is present in all these patients during digitalis slowing, observations are still insufficient to determine the percentage of cases so influenced or the precise degree in which the two factors are called into play. To embrace all cases of auricular fibrillation, our conclusion must remain tentative. We may sum up by stating that in the light of experimental and clinical observations it seems clear that digitalis exerts a twofold action, a direct and an indirect one, both of which decrease the facility with which impulses are conveyed across the *A-V* junction; both of which therefore reduce the rate of the responding ventricle. A similar conclusion has been reached by Robinson and Wilson[14] arguing from experimental data, and by Cohn[1] who argues mainly from clinical data. The proportion in which these two actions are exerted is probably variable in cases of fibrillation of the auricle; in some cases the vagal action appears to be the more conspicuous factor; in others, very probably, the direct action is predominant.

The importance of these conclusions will become more evident when we study the action of digitalis upon the auricle in auricular fibrillation.

Action upon the Fibrillating Auricle. Generally speaking it has been assumed that in cases of auricular fibrillation, exposed to the influence of digitalis, the auricular action remains constant, and that the whole effect upon the ventricular rate is localized in the junctional tissues. This is not strictly true; for the auricle is also affected. The action is not an entirely constant one, but in the majority of patients the oscillations recorded from the auricle are decidedly increased in rate (Figs. 2, 3 and 4). This change is studied in curves taken by means of direct leads from the chest wall, in which curves the electrical events in the auricle are represented in a comparatively pure form. Of 11 cases investigated, the oscillations showed no appreciable change of rate in 3 cases;

in 1 case there was a fall of rate; while in the remaining 7 cases there was a decided or conspicuous rise of rate; in 2 cases the rise amounting to 60 or 70 beats per minute.

To what is this usual rise of rate due? To answer this question we must clearly understand the nature of auricular fibrillation. This mechanism, according to the theory we support, is the result of a continuously circulating wave in the auricle. The circus movement controls the rate of the auricular oscillations, each oscillation corresponding to a complete auricular circuit. The time in which these circuits are completed actually depends upon two factors, (*a*) the length of the path followed and (*b*) the rate at which the wave travels. But the length of path is itself controlled by the length of the refractory period at any one point in the muscle and by the rate of conduction. Consequently we may say that the time in which a circuit is completed is controlled by two factors, namely, (1) the length of the refractory period and (2) the rate of conduction. As the rate of the oscillations per minute is due to the duration of individual circuits, it will be evident that the rate of oscillation is controlled by the same two factors.

A lengthening of the refractory period, by lengthening the path, will tend to increase the duration of each circuit and will slow the oscillations. Conversely, a shortening of the refractory period will tend to accelerate the oscillations.

Slowing of conduction will lengthen the circulation time and decrease the rate of oscillations; quickening of conduction, will increase the rate of the oscillations.

Now digitalis has two effects on the heart muscle. Insofar as it acts by increasing vagal tone it will reduce the length of the refractory period and it will tend to increase the rate of conduction. Thus, a vagal action of digitalis theoretically will reduce the time of circulation, will increase the rate of the oscillations. In experiment, vagal stimulation is well known to exert this influence upon the oscillations of a fibrillating auricle.[10] [15]

On the other hand, digitalis, acting directly on the muscle, increases the length of the refractory period and retards conduction.[11] Theoretically, this direct action will increase the duration of the circulation time and slow down the oscillations. In anesthetized dogs, when a drug of the digitalis group is given, the vagal part of the drug's action is usually little in evidence, the chief action is a direct action. In such, the injection of the drug tends, as is expected, to slow the oscillations of the auricle which has been forced to fibrillate.

It is to be remarked that, when we are dealing with the rate of ventricular beating, both the direct and indirect actions of digitalis are exerted in the same direction, *i. e.*, toward ventricular slowing. But in the case of the fibrillating auricle, the direct and in-

direct actions are opposed to each other, and may in large part neutralize each other.

Because in actual observation we find it to be the rule that the auricular oscillations are increased in rate, it seems impossible to avoid concluding that the predominant action of the drug is through the vagus, so far at least as the auricle is concerned. The nature of the *A-V* block resulting from digitalis has been discussed and the observations of Cushny have been revised, mainly because, if his conclusion that this action is purely a direct one in cases of fibrillation of the auricle is correct, it would stand in conflict with what appears to be the inevitable conclusion in the case of the auricle itself. The revision of his work on the ventricle has led us to a conclusion which is compatible with the observations upon the auricle. Both the direct and indirect factors come into play. Just as in the case of the ventricle, so in the case of the auricle, the proportion between the direct and indirect actions is variable. In the case of the auricle, in virtue of the fact that the two effects of digitalis are manifested in opposite directions, it is an easier matter to ascertain their proportion than is the case with the ventricle, where the two effects are manifested in one and the same direction. An increase in the rate of the auricular oscillations, which appears to be the rule, signifies predominant vagal action; a decrease, which is sometimes seen, indicates a predominant direct action; unaltered rate indicates a balance between the two influences.

Conversion of Flutter into Fibrillation by Digitalis. In 1911 Mackenzie[12] reported two cases of paroxysmal tachycardia, in both of which digitalis appeared to exercise a beneficial effect. The tachycardia, in each case of obscure form, gave place to fibrillation of the auricles under digitalis, and subsequently a normal rhythm was resumed. In the first of these cases, historically the more important of the two, I took electrocardiograms from the patient during his period of tachycardia. These curves I was at the time unable correctly to interpret, but they were published in Mackenzie's paper.

In the following year I was able to report upon a similar case in which a long-continued tachycardia was converted by the action of digitalis into fibrillation of the auricles with a subsequent resumption of the normal rhythm;[7] and was able to identify the original tachycardia of this case with those previously reported by Hertz and Goodhart[5] and Jolly and Ritchie,[6] and termed by the latter writers "auricular flutter." The observations upon this case further enabled me in the same article to place a final and correct interpretation upon the case reported by Mackenzie; it became evident in the light of the new case that Mackenzie's case had also been one of flutter. A series of cases in which a similar

reaction to digitalis was observed was reported at a later date[9] and was soon followed by confirmatory observations by Ritchie and others.[13] The curious reaction, by which flutter of the auricle is converted to fibrillation, soon became well known and is now widely recognized. So far, however, it has not been explained.

The chief differences between clinical flutter and fibrillation, which have as yet been established, are that in the last condition the oscillations are more rapid and that they have not the regular incidence of those seen in flutter. According to our views the first difference may be interpreted to mean that the circuit movement is completed more rapidly, the second difference is due to irregular conduction in the case of fibrillation. What is the underlying cause of these differences? On this question it is still impossible to speak with certainty. The rapidity with which the circus movement is completed in fibrillation may be due either to more rapid conduction or to a shorter path.

It is very difficult to assume the first for several reasons. In general, the more rapidly an auricle beats, the slower will its tissue conduct, so that actually we should expect fibrillation to be associated with slower and not with faster conduction. If we were dealing with fibrillation in one patient and flutter in another, this argument would lose much of its force; but we have to face the fact that both flutter and fibrillation may occur as stable mechanisms in one and the same patient, under surrounding conditions which appear to be identical. Thus flutter, which has long been stable, may be converted into fibrillation by digitalis, and this may and often does continue as a stable mechanism, long after the action of digitalis has passed away. The reverse change may sometimes be accomplished by the use of quinidine. It is difficult to believe that the rate of conduction (at a given rate of beating) is permanently altered as an after-effect of administering one or other of the drugs. A second argument against faster conduction in fibrillation, is the irregularity of conduction, such irregularity being known to result when the conduction power is pressed to its utmost and is at its slowest. We are, therefore, probably correct in assuming that conduction is slower in the fibrillating auricle than in the fluttering auricle; but this difference fails to explain why the rate of oscillation is higher in fibrillation than in flutter; we turn to the alternative.

Does the difference consist in the length of path followed, the path being shorter in fibrillation than in flutter? Here again we have no direct and conclusive evidence, but there is some which is very suggestive. If we exclude faster conduction in fibrillation, then a shorter path may be due to shortening of the refractory period, it being assumed that in fibrillation the crest of the circulating wave always follows closely on the wake of retreat; in

these circumstances the actual length of path would be controlled by the length of the refractory period, the wave at once entering muscle in which recovery is expedited. This view, that the refractory period in fibrillation is less than in flutter, has been put forward already by Rothberger and Winterberg, for it is consistent with the known relation between refractory period and rate of beating, the former becoming of shorter duration as the rate rises.

The path in fibrillation may be shorter than in flutter for another reason. In the first condition we conclude that the gap between the crest of the wave and its wake is a very short one; and we come to this conclusion because conduction is irregular in fibrillation and the path varying. In flutter, on the other hand,

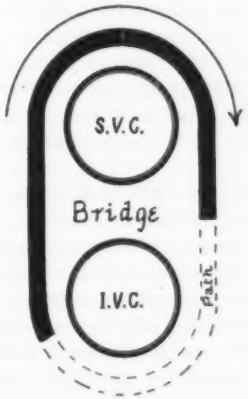

FIG. 5.—A diagram of circus movement around the superior and inferior vena cava, to illustrate how, when an appreciable gap exists, the wave may be unable to pursue a shorter course between the cavæ, unless the refractory period shortens. The diagram and its explanation suggest why the passage of flutter to fibrillation, or the reverse passage, should be an abrupt one.

the rate of conduction is constant and the path unvarying; this difference in the two mechanisms is consistent with the view that while the gap is short in fibrillation it is longer in flutter; the wave would then enter tissue in which an appreciable time for recovery has elapsed, whereby recovery of the tissue functions is carried further and to a more uniform point. Now a longer gap, other conditions being equal, would mean a longer path and a slower circulation time. Thus the essential distinction between fibrillation and flutter may consist in the length of the gap. This assumption would certainly seem to explain the observed differences between the two disorders.

If we accept this idea as a working hypothesis, it follows that

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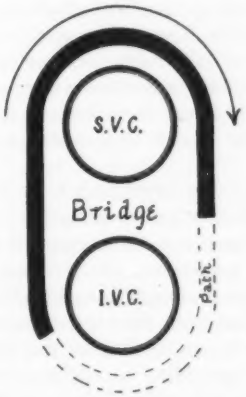

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the path travelled in flutter is compulsory to this extent, that the head of the wave is unable to make a short cut and thus to approach more closely to its own wake. To explain this conception in more detail, imagine the wave in flutter to be circulating around the mouths of both superior and inferior vena cava (Fig. 5). Such a circulating wave may exist in a stable form although a considerable gap exists. It cannot take the short path between the two cavæ, for whenever its crest reaches this muscle bridge, it will find muscle on this cross-route refractory. But supposing that this is the state of affairs, and at a given moment the refractory period of the muscle shortens; the bridge may then be passed and the wave will then circulate, with a much shortened gap, around one or the other cava. The circulation time will decrease and, as a consequence, the refractory period will shorten a little more, tending to secure stability in the new mechanism, even when the original influence which shortens the refractory period is withdrawn. But as the gap is now smaller, conduction will tend to be more irregular and a little slower. In some such fashion it seems probable that the change from stable flutter to a more or less stable fibrillation may be produced.

Support is given to this argument by the change from stable fibrillation to stable flutter under quinidine. Hitherto, the significance of this change seems to have escaped notice. If the quinidine is given to these patients, a state closely resembling what we formerly termed flutter is always brought about, and this has been noted by several workers; but that is not the whole story. Usually the state produced is in reality impure flutter and this disappears invariably when the quinidine is withdrawn and its temporary effects on conduction and refractory period disappear. But in one patient in ten or more, pure flutter becomes established under quinidine; if now no further quinidine is given, the flutter does not disappear, it remains as a stable condition.

In the period of quinidinization, the refractory period is lengthening out and the rate of oscillations is falling. There comes a time when the reaction is at its height and the refractory period is at its longest; it is at this stage that pure flutter appears. We withdraw the quinidine and, as experience tells us, the refractory period recovers after a few (twenty-four to forty-eight) hours. Simultaneously any effect which the drug exerts on conduction must disappear. Thus, although both factors which tended to produce slowing of the oscillations disappear, little acceleration is apparent. A second and new condition of stability is reached. There is here little escape from the conclusion that the circuit contains a longer gap; such a gap must appear as recovery takes place without a corresponding speeding up of the movement. If similar doses of quinidine are repeated on this same patient when the flutter has

become quite stable, considerable doses may be given without appreciably affecting the rate of oscillation. There is some slowing, but this is minor in its degree and is to be attributed to the effect of the drug on conduction alone. It is comparable to the slight acceleration which occurs before the flutter becomes stable, a change due to improved conduction following withdrawal of quinidine. The delay of a pronounced fall in rate when the auricle is fluttering is due to the period occupied by closure of the gap by the lengthening refractory period.

Thus, we may conclude that one essential difference between flutter and fibrillation is that the gap is longer in the former.

We now return to the original question; and ask why digitalis converts flutter into the faster-moving fibrillation? Whether the reply is that it must quicken conduction, or whether the reply is that by reducing the refractory period it shortens the path upon which the wave circulates—and the latter is the more promising hypothesis—the explanation of its action will take the same direction; it will be necessary to assume that the quickening is due to a predominant action through the vagus nerve. Just as we explain an increased rate of oscillation in fibrillation itself consequent upon digitalis, so we explain the conversion of flutter in fibrillation; the vagal component of digitalis action will alone induce those changes in the muscle which are theoretically necessary to bring about the quickening which occurs. If you so desire, you may treat the question more upon the lines of direct observation. A material increase of vagal tone quickens the rate of experimental flutter and eventually may force it into fibrillation;[13] [15] actually the effect of the direct action of a digitalis body upon flutter has not yet been observed, but we can predict that it would not quicken the movement, for in experiments on dogs, under certain conditions of anesthesia, in which the direct action is alone displayed and the auricles are fibrillating, quickening does not occur; on the contrary, slowing is often seen.

We need therefore have little hesitation in concluding that the conversion of flutter into fibrillation by digitalis is essentially vagal in origin.

The Influence of Auricular Quickening upon Ventricular Slowing under Digitalis. As stated, it has generally been assumed that when the auricles are fibrillating, the effects of digitalis upon the ventricle result simply from heart-block. This assumption is not in the strictest sense justified; for it is the rule to find that when the ventricle slows, the auricular mechanism also changes; in greater or lesser degree the movement quickens, and this quickening will exert some influence upon the rate of the ventricular response. Experiments bearing upon this point of view show that at fast rates of beating an increase of rate in the auricle tends in

itself to lower the rate of ventricular response; it favors block. The degree in which this influence is responsible for the ventricular slowing cannot be considered in detail on the present occasion. It must suffice if I say that, considering the relatively small change of rate which occurs in the auricle, we do not consider the influence to be a very material one at the rates prevailing.

It is to be noted also that atropine when given in cases of fibrillation produces a fall of auricular rate. This fall of rate will in a small measure favor a rise of ventricular rate, usually attributed entirely to removed vagal tone; the fall of auricular rate is usually small, and is not very materially different in digitalized and undigitalized cases; so that this effect has been neglected in the argument of this article. The magnitude of another factor in the action of atropine is less certain; in experimental fibrillation, if strophanthin is injected and produces a little slowing of the ventricle by a *direct action* rather than by a vagal action, an event which often occurs in dogs under full anesthesia, then a full dose of atropine does not increase the rate of the ventricle but may appreciably *decrease the rate.* If digitalis acted directly upon the muscle in man, and only directly, it seems probable that a similar decrease of ventricular rate with atropine would sometimes be seen in patients; actually this is not the case.

A final word completes what I have to say: It seems to us that the more we explore the facts and view them in the light of the theory of circus movement, as the fundamental cause of flutter and fibrillation, the more clearly is our whole knowledge of flutter and fibrillation illuminated. We cannot believe that the theory would be found to offer a reasonable interpretation of so many and such diverse phenomena unless it were fundamentally true.

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THE SPLEEN AND DIGESTION.

Study III. The Spleen in Inanition; The Effect of the Removal of the External Secretion of the Pancreas on the Spleen.*

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The spleen atrophies in inanition. Some observers have believed this to bespeak a part for the spleen to play in the temporary storing of protein food materials, analogous, in a way, to the part played by the liver in the storage of glycogen.

A functional interrelationship between the spleen and the pancreas, asserting itself especially during the digestive period, has been believed to exist by many investigators. This idea has found chief expression in the theory first put forward by Schiff, in 1862, and later championed by Herzen, that the spleen forms a product of internal secretion which can change trypsinogen into trypsin.

A striking simple atrophy of the spleen following complete removal of the external secretion of the pancreas has recently been reported by Sweet and Ellis. This atrophy, they believe, is greater than can be explained by the loss in body weight occurring under such circumstances. If this be true, it has direct bearing on the part of the spleen in digestion, and is suggestive of a specific pancreatic splenic interrelationship.

The investigation of the Schiff-Herzen hypothesis by determining the influence of splenectomy on pancreatic secretion has been reported in Study II of this series. In the present study further data on the splenic atrophy occurring in inanition will be presented, and the question of a suggested influence of the pancreas on the spleen will be approached by a repetition of the observations of Sweet and Ellis.

The spleen is an unusually variable organ. Its normal size in different animals is markedly fluctuant. Its weight in proportion to body weight varies not only in genera and species, but also in the individual. It changes its volume on slight provocation, and is highly susceptible to hypertrophy and atrophy. Therefore, conclusions drawn from changes in the size of this organ must be carefully checked.

In death from starvation the body weight of mammals is reduced two-tenths to four-tenths in the young and four-tenths to

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five-tenths in the adult (Fredericq and Nuel). The percentage losses of various tissues and organs in the cat are: fat, 97 per cent; spleen, 66.7 per cent; liver, 53.7 per cent; muscles, 30.5 per cent; blood, 27 per cent; intestines, lungs and pancreas, 17 per cent; bone, 13 per cent; central nervous system, 3.2 per cent; and heart, 2 per cent (Voit).

The effects of inanition in albino rats have been studied exhaustively by Jackson. He found apparently a decrease in weight of the spleen of 51 per cent in acute inanition and of 29 per cent in chronic inanition. He states, "That the spleen loses heavily during inanition, losing in relative as well as absolute weight has been found in man (Aschoff '11; Stschorstuy, 1898), pigeon (Chossat, '43), rabbit (Bowin, '90), and cat (Voit, '66; Sedlinair, '99), while a decrease less marked than in the whole body (relative increase) appears in the dog (Falck, '54) and in thin steers, compared with fat (data from Missouri Agricultural Experiment Station). Data from von Bechterew ('95) indicate a relative increase in the spleen of newborn kittens during inanition, but a decrease in puppies. These apparently conflicting statements are perhaps to be explained largely by the great variability of the spleen, making comparisons with controls uncertain. In addition, however, there is the possibility that the loss in the spleen may vary according to the character and stage of inanition. Thus Sasarew ('97) in the guinea pig found the greatest loss in weight of the spleen to occur in the middle period of inanition (second period of 10 per cent loss in body weight)."

An interesting necropsy on a tailor who refused all food and died on the sixty-third day has been reported by Mayers. The spleen was small and shrunken with a wrinkled capsule; it was pale and flabby and weighed only 53 gm. The body weight at death was about 80 pounds; he had lost 40.7 per cent of his original weight. If the spleen normally was of average weight it must have given up excessively of its substance. Microscopic examination of the organ revealed almost complete absence of the corpuscles, the distribution of many erythrocytes around the parenchyma and little evidence of the presence of the splenic sinuses.

The histologic changes occurring in the spleen of the cat and of the guinea pig in acute starvation have been studied by Jolly and Levin. They found a thinning of the pulp cords and a reduction in the number of lymphocytes. The venous sinuses were often filled with large phagocytic cells stuffed with erythrocytes.

The observation that an excessive shrinkage of the spleen occurs when the external function of the pancreas is removed was reported in a brief communication by Sweet and Ellis in 1915. They resected the duodenal portion of the pancreas in dogs, or ligated the pancreatic ducts, or cut them with the interposition of omentum between the gland and the gut. Thus the internal function of the

pancreas was still provided for and glycosuria did not develop. The animals had voluminous fatty stools, and at first lost weight rapidly; however, after several months they reached a stationary weight or even gained slightly. The change noted in the spleen consisted apparently of a simple atrophy, and was marked after three days. Control experiments in animals with equal loss of weight were not performed.

Sweet has suggested that there may be a possible surgical bearing of this relation between the pancreas and the spleen. He cites the report of Musser of an acute anemia in four of eight cases of acute pancreatitis. In view of the generally accepted relation of the spleen to the blood, he considers his finding of an acute splenic atrophy under the conditions citied as suggestive of an explanation of Musser's report of acute anemia, and as furthermore suggestive of the importance of clinically following the blood picture in cases of suspected or proved acute pancreatitis.

Animals deprived of sustenance are obliged to draw on their own storehouses and their own tissues for food. Yet dearth of aliment not alone leads to inanition, for non-assimilation, even though food is taken in the greatest of plenty, attains a similar end. If pancreatic juice is excluded from the intestine there is a marked diminution in the absorption of nitrogen and fat, as has been demonstrated by Pratt, Lamson and Marks. This results in an immediate disturbance in metabolism with loss in body weight. May not then the dwindling of the spleen in animals in which the external function of the pancreas has been removed be merely the expression of the ease with which this organ gives excessively of its substance when the body labors under nutritional deficiency? May it not be merely the atrophy of the spleen of inanition?

Most comparative studies of the changes in weight of organs have been made by checking the findings of the abnormal states with the findings under normal conditions in individuals of the same species. In the case of the spleen this method is fraught with great error attributable to the protein habits of this most mysterious and changeable organ. Hence, in the gathering of experimental data in answer to the above question complete observations should be made on one and the same animal in each instance.

Experimental Methods and Data.—In adult dogs complete removal of the external secretion of the pancreas was obtained by resection of the duodenal portion of the gland with tying off securely the severed ends of the remaining pancreas after the manner of Sweet and Ellis or by double ligation of the pancreatic ducts. Observations were also made on dogs with pancreatic fistulas complicated in most cases by pancreatitis. These animals were kept on full diet. As controls, dogs were fed a half-day's ration every third day and fasted in the interval. The size of the spleen was determined

at the start and at the end of every experiment. Microscopic sections of the spleen and pancreas, and often also of other organs, were made.

The initial splenic weight was determined as follows: Measurements of the total length, of the width of the head and of the tail, and of the thickness of the spleen were made by a movable centimeter scale. For the head the measurement of greatest width was taken; for the tail a transverse line was drawn through a point on the longitudinal axis of the organ (this point was placed at such a distance from the caudal extremity as to represent a certain fraction of the total length of the spleen); and for the thickness, a line was drawn at the middle of the gland running from the hilus perpendicularly to the broad free splenic surface.

The body, and thus the major portion of the spleen of the dog, most nearly resembles a rectangle in outline; the head is increased in width at one side and tapers at the tail; a cross-section at most points is triangular with the apex at the hilus. Therefore, because of its form, the exact computation of the volume of the spleen is not feasible from the measurements taken. However, since weight, the final value of which is easily determined at necropsy, serves our purpose even better than volume, the use of proportion will permit us to make an approximate estimation of the initial weight of the spleen without knowing the exact splenic volumes.

If changes in specific gravity are disregarded for the time being the proportion as follows will hold: $x : a :: y : z$. (in which x = initial splenic weight, a = final splenic weight, y = initial splenic volume and z = final splenic volume).* Since the splenic volumes are unknown as well as the value of x, we may substitute for y and z in the proportion the volumes of similar rectangular parallelopipeds (for the volumes of similar irregular solids are proportional to the similar regular parallelopipeds most nearly approximating their own shape) which can be determined from the measurements given. In the present study the lengths and thicknesses of the spleens and the means of the widths of their heads and tails have been taken for the dimensions of the parallelopipeds. If then b is taken as the volume of the parallelopiped corresponding to the initial size of the spleen and c as that corresponding to the final size, these known values may be substituted for y and z in our proportion, which will then read: $x : a :: b : c$.

However, the values thus determined for x do not take into account changes in specific gravity. In three of the spleens in this series the specific gravity (determined by Hammerschlag's method) was found to be approximately 1.060 for the normal and 1.070 in inanition. There were but small changes from this latter figure with lesser or greater lengths in the periods of loss of weight,

* The author is indebted to Mr. H. O. Stearns of the Mayo Clinic for suggestions regarding the mathematical procedure used in this method.

the spleen evidently losing very rapidly of its fluids in acute inanition. Therefore in the values given for the initial weights of the spleens this correction for change in specific gravity has been made, that is, the initial weights have been multiplied by the factor 0.99.

Histologic Changes.—*The Spleen.* The histologic changes in the spleen, found in these experiments, appeared similar, regardless of the procedure employed, so long as loss of body weight occurred. In the instances in which the experiments were prolonged for fifty days or longer the microscopic picture seemed identical in the fasting animal and in the animal deprived of the external secretion of the pancreas. Therefore the histologic findings will be given in one description.

Changes in the spleen were observed as follows: The capsule was shrunken, wrinkled and much decreased in width; its fibrous tissue strands were compact, giving at times an almost hyaline appearance; nuclei were less abundant and the few scattered lymphocytes usually seen were absent. The shrinkage in the splenic septa was not so noticeable. The parenchyma, however, was quite decreased in amount, so that comparatively the septa stood out as more numerous than normal. In the splenic pulp the cells often were packed almost as closely as in the normal Malpighian corpuscle. The tissue spaces were largely obliterated. The cytoplasm of the pulp cells and pulp supporting tissue had largely disappeared, and the nuclei, closely crowded, chiefly remained. The splenic sinuses, although diminished in size, often stood out clearly; the amount of blood they contained was less than that seen in a normal section. The number of lymphocytes outside the Malpighian corpuscles was markedly decreased; cells of large type predominated. The Malpighian corpuscles themselves and their germinal centers seemed more definitely delimited than usual. The larger bloodvessels of the gland appeared but little altered. There was constantly more free blood pigment in the pulp than normal.

The degree of these changes seen in the spleen was roughly proportional to the length of the experimental period and to the acuteness with which loss of body weight occurred. The changes themselves were such as those ascribed to a simple atrophy of the gland.

The Pancreas. In the instances in which a partial pancreatectomy was performed, or the pancreatic ducts were ligated, varying degrees of destruction of the pancreatic acini and their replacement by connective tissue occurred, depending on the length of time of removal of the external function of the pancreas with the resultant obstruction of the pancreatic ducts. In the most acute experiments merely a decrease in the clearness of the staining reactions or a beginning necrosis was seen. In the prolonged

experiments very little acinar tissue was left. The pancreatic ducts and their larger ramifications were in most instances dilated to three or four times their normal size.

In those cases in which pancreatic fistulas were performed without infection no damage to the acinar tissue occurred. However, generally a complicating purulent pancreatitis, of varying intensity and acuteness, was present.

Protocols.—All operative procedures on the experimental animals were performed under ether anesthesia with the employment of

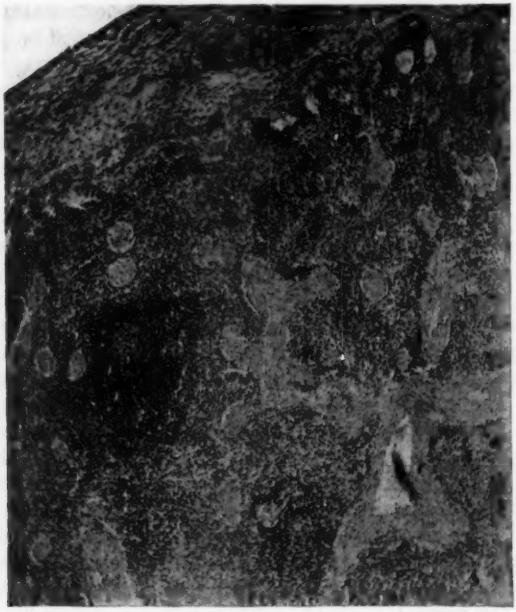

FIG. 1.—D 537. Ligation of pancreatic ducts. Normal spleen at the beginning of the experiment. Photomicrograph × 50.

sterile technic. In none of the dogs in which the external function of the pancreas was removed did glycosuria appear; all, however, had fatty stools.

Ligation of Pancreatic Ducts.—D 537, a male mongrel in good condition. April 23, 1920, both pancreatic ducts were doubly ligated and divided. The animal gradually lost 2.6 kg. during the first month and then became stationary in weight till the ninth week, when symptoms of inanition appeared. From this time there was a rapid and progressive loss. July 27 the dog was killed

by etherization. At necropsy very little pancreatic tissue could be found. The pancreatic ducts were not dilated. Histologically the pancreas consisted almost entirely of connective tissue, although a few areas were still present containing islets of acinar tissue (Figs. 1, 2 and 3).

Resection of Duodenal Portion of Pancreas.—D 648, a male mongrel in good condition. April 30, 1920, the duodenal portion of the pancreas was resected. The animal made an excellent recovery and maintained its weight for one week. During the next three

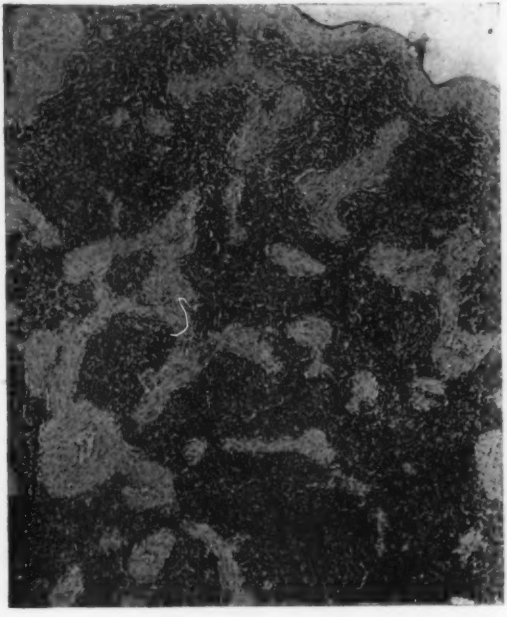

FIG. 2.—D 537. Ligation of pancreatic ducts. Spleen at the end of the experiment. Photomicrograph × 50.

weeks there was a loss of only 1 kg.; following this there was a progressive and steady decline in weight. July 22, the dog was killed by etherization. At necropsy all the tissues seemed to be anemic; save for a few small islets the pancreatic glandular tissue had disappeared. The pancreatic ducts were distended to about six times their normal size. It was difficult to identify the splenic sinuses histologically; they appeared almost obliterated. The pancreas was fibrous.

D 649, a male mongrel in good condition. April 30, 1920, the

duodenal portion of the pancreas was resected. The skin incision became infected and did not heal. Later, distemper developed. The dog lost weight rapidly and progressively from the time of the operation. It was killed by etherization May 17. At necropsy a diffuse pancreatic fat necrosis was found. Histologic examination revealed much free blood pigment in the spleen. The pancreas was necrotic. There were areas of bronchopneumonia in the lungs.

D 661, a male poodle in fair condition. May 7, 1920, the duodenal portion of the pancreas was resected. The animal recovered

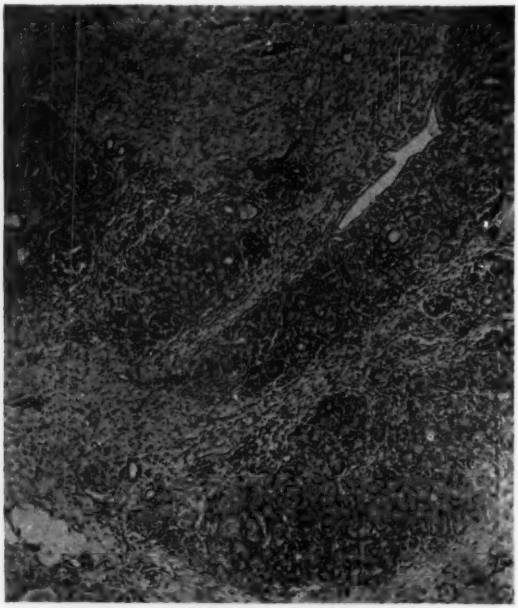

FIG. 3.—D 537. Ligation of the pancreatic ducts. Pancreas showing fibrosis and remaining islets of acinar tissue at the end of the experiment. Photomicrograph × 50.

well, but lost weight steadily until the last eleven days before death, when the weight became stationary. July 2, the dog was killed by etherization. At necropsy very little pancreatic tissue was found. The pancreatic ducts were dilated to about four times their normal size. The section of the spleen removed at operation for histologic study contained a number of large multinucleated cells. Only a few of these could be seen in the section from the specimen removed at necropsy. There was a marked collection of blood pigment in the pulp of the atrophic spleen. In the pancreas a small amount of acinar tissue was left in islets (Figs. 4 and 5).

D 698, a female terrier in good condition. May 27, 1920, the duodenal portion of the pancreas was resected. The spleen was large for the size of the dog and grossly pathologic; it was cirrhotic and contained numerous small infarcts. The animal developed distemper almost immediately and was killed by etherization May 31. At necropsy marked purulent conjunctivitis, rhinitis and tracheobronchitis were present. The abdominal wound was infected superficially and showed no evidence of healing. There was a slight degree of pancreatic fat necrosis in the omentum

FIG. 4.—D 661. Partial pancreatectomy with loss of external secretion of pancreas. Spleen at the end of the experiment. Photomicrograph × 50.

around the ends of the severed pancreas. The pancreas itself was indurated as if it had been in fixing fluid. There were no findings to explain the original pathologic condition of the spleen. Histologic examination did not reveal changes in the spleen or the pancreas.

Pancreatic Fistula Complicated by Infection.—D 720, a female mongrel in excellent condition. June 12, 1920, a one-stage operation for pancreatic fistula was performed. An accessory spleen 0.45 cm. in diameter was found in the omentum 7 cm. from the hilus of the major spleen. The animal refused all food, and milk fed

through the stomach tube was vomited. An irritative pancreatic secretion appeared and the animal thus continuously lost large quantities of pancreatic juice. The last four days preceding death, which occurred July 2, a marked inanition supervened. At necropsy a non-purulent infection involving the transplanted portion of the pancreas was found. A large amount of subcutaneous fat was still present, but the animal was extremely dehydrated. The accessory spleen was atrophic with a diameter of 0.34 cm., thus having lost 43 per cent in volume.

FIG. 5.—D 661. Partial pancreatectomy with loss of external secretion of the pancreas showing destruction of acinar tissue with fibrosis and a dilated pancreatic duct. Photomicrograph × 50.

D 743, a male bull terrier in fair condition. June 19, 1920, a one-stage operation for pancreatic fistula was performed, with ligation of the minor pancreatic duct. The wound became infected superficially and was slow in healing; the animal steadily lost weight and became extremely emaciated, and there was a marked continuous irritative secretion of juice from the fistula. The animal died July 14. At necropsy a purulent pancreatitis was found.

TABULATION

Animal.	Duration of experiment, days.	Initial body weight, kg.	Final body weight, kg.	Total change in weight, kg.	Length of spleen, cm.		Width of spleen, cm.				Thickness of spleen, cm.		Initial weight of spleen (approximate), gm.	Final weight of spleen, gm.	Spleen: initial percentage of body weight (approximate).	Spleen: final percentage of body weight.	Percentage of change of body weight.	Percentage of change of weight of spleen. (approximate).	Procedure.
							Head.		Tail.										
					Initial.	Final.	Initial.	Final.	Initial.	Final.	Initial.	Final.							
D 698	4	9.5	8.5	−1.0	15.8	13.8	4.1	3.3	3.5	3.3	1.3	1.2	52.3	37.0	0.550	0.435	−10.5	−29.8	Partial resection of pancreas (distemper).
E 129	4	19.6	16.8	−2.8	16.0	15.5	7.1	4.6	4.0	3.3	1.3	0.8	73.2	32.6	0.373	0.194	−14.3	−55.5	Pancreatic fistula (peritonitis).
E 131	15	10.0	7.6	−2.4	14.2	14.2	5.3	4.0	4.0	2.3	0.8	0.7	30.5	18.3	0.305	0.240	−24.0	−40.0	Pancreatic fistula (pancreatitis).
D 649	17	7.0	4.8	−2.2	11.1	10.6	3.1	2.6	2.6	2.1	0.7	0.4	14.5	8.0	0.207	0.166	−31.3	−45.0	Partial resection of pancreas (pancreatic fat necrosis; distemper).
D 730	20	11.7	8.2	−3.5	10.9	9.8	3.8	2.1	2.9	1.8	1.1	0.6	29.0	8.5	0.248	0.104	−29.9	−70.7	Pancreatic fistula (pancreatitis).
D 743	25	19.6	12.4	−7.2	17.6	15.8	6.1	4.5	4.0	2.8	1.4	1.1	72.3	33.8	0.369	0.273	−36.7	−53.0	Pancreatic fistula; ligation of minor pancreatic duct (pancreatitis).
D 130	28	10.2	10.6	+0.4	13.8	15.2	4.8	4.6	4.0	3.4	1.0	1.0	28.47	28.5	0.279	0.269	+ 3.9	+ 0.1	Pancreatic fistula.
D 876	51	9.4	6.4	−3.0	11.9	9.8	5.9	4.0	2.0	1.7	0.8	0.6	20.0	10.0	0.213	0.156	−31.9	−60.0	Fasting.
D 875	51	13.0	7.0	−6.0	11.7	8.0	6.7	4.3	2.5	1.6	2.2	0.7	56.4	7.8	0.433	0.111	−46.2	−86.1	Fasting.
D 661	55	13.8	7.8	−6.0	17.0	10.4	4.5	2.3	4.0	2.0	1.4	0.7	70.0	10.5	0.508	0.350	−43.5	−85.0	Partial resection of pancreas.
D 648	82	14.1	8.6	−5.5	11.4	8.6	5.2	4.5	3.1	2.1	1.0	0.5	29.7	9.0	0.248	0.105	−39.0	−70.0	Partial resection of pancreas.
D 537	96	17.6	9.7	−7.9	14.1	11.4	4.8	3.0	4.4	2.4	1.0	0.8	40.5	16.0	0.287	0.165	−44.5	−60.5	Ligation of pancreatic ducts.

E 131, a male mongrel in good condition. December 7, 1920, a one-stage operation for pancreatic fistula was performed. The wound became infected and a continuous irritative secretion of pancreatic juice appeared. The animal refused food and lost weight rapidly. Death occurred December 22. Pancreatitis was found at necropsy. The initial specific gravity of the spleen in this instance was 1.061, that at death 1.073.

E 129, a male shepherd in good condition. December 7, 1920, a one-stage operation for pancreatic fistula was performed. The

FIG. 6.—D 875. Fasting. Spleen at the end of the experiment. Photomicrograph × 50.

animal became extremely ill and died December 11. At necropsy a generalized peritonitis with a small amount of sanguinopurulent fluid in the peritoneal cavity was present. The initial specific gravity of the spleen in this instance was 1.062; that at death, 1.070.

Fasting.—D 875, a male bull terrier in good condition. August 6, 1920, the abdomen was opened and measurements of the spleen taken. The animal was then fed a half-ration every third day and fasted in the interval. Save for a slight gain at the end of one and a half weeks and a stationary period from the seventeenth to the twenty-sixth day the animal lost weight progressively. September

28, splenectomy was performed. Death occurred two days later, probably as a result of the operation and the dog's weakened condition. A section of the spleen at the first operation had many multinucleated giant cells, and free blood pigment was present in the pulp. A section of the spleen at its removal showed changes identical with those occurring after removal of the external secretion of the pancreas. The amount of free blood pigment was increased. No multinucleated giant cells could be found (Fig. 6).

D 876, a male mongrel in good condition. August 8, 1920, the abdomen was opened and the spleen measured. The animal was then fasted in a manner similar to D 875. The weight from the twelfth to the twenty-sixth day remained constant, but steadily decreased at all other periods. September 28, splenectomy was performed. The dog made a good recovery. The histologic changes in the spleen were those of a simple atrophy.

Uncomplicated Pancreatic Fistula.—E 130, a female mongrel in good condition. December 7, 1920, a one-stage operation for pancreatic fistula was performed. Recovery was excellent and the wound healed without infection. Secretion of juice from the fistula was normal. The animal was carefully fed and gained weight slightly. January 4, 1921, the spleen was removed, without incident. The initial specific gravity of the spleen was 1.061; that at the time of splenectomy was 1.060. The splenic measurements remained practically the same.

Discussion.—The size of the spleen of the dog varies greatly; in this series of experiments it fluctuated between 0.2 and 0.55 per cent of the body weight, with an average of about 0.3 per cent.

The data submitted justify the conclusion that the spleen loses markedly in weight in inanition and are in general corroborative of the findings of other investigators. The loss in the weight of the spleen is out of all proportion to the decrease in body weight, being almost three times as great as a maximum in extreme cases of acute inanition, and approximately twice as great in cases of less acute.

The removal of the external function of the pancreas by ligation of the pancreatic ducts or resection of the duodenal portion of the gland likewise leads to an excessive decrease in the size of the spleen. This finding thus confirms the observations of Sweet and Ellis. However, the shrinkage of the spleen under these conditions can be explained as due to the inanition resulting from the exclusion of the pancreatic juice from the intestine, and does not require for its elucidation the postulation of a specific pancreatic splenic interrelationship.

The loss of weight of the spleen in relation to the loss of body weight in these experiments is shown graphically in Figure 7. It will be noted that the greatest loss of weight both of the body and of the spleen occurs within the first month. The diminution of

the weight of the spleen is especially rapid during the first few days of inanition. The chart indicates also how markedly the percentage splenic weight fluctuates from the normal in contradistinction to the percentage body weight, which shows relatively little such fluctuation.

That the marked atrophy of the spleen under the experimental conditions of this study is nothing more than the mere expression of the disproportionate share of the gland in the general loss of weight is shown by a comparison of the experimental results in the cases of Dogs D 661 and D 875, the former representing a

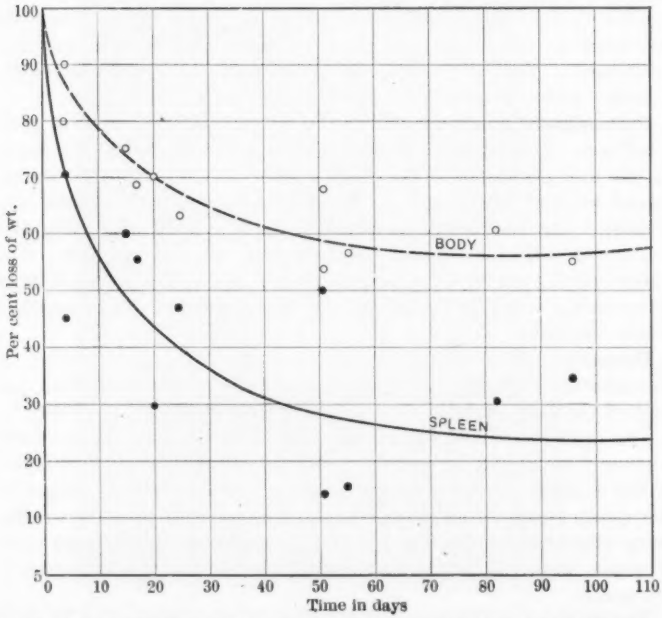

FIG. 7.—Graphs illustrating the percentages of losses of weight of the body and of the spleen in relation to the length of the inanition period. (See table.)

partially pancreatectomized animal and the latter a control under starvation. Both animals weighed approximately 13 kg. and lost about 45 per cent of their body weight within a period of fifty days, whereas their spleens each lost about 85 per cent of their original weight. These are the most marked losses in weight obtained, but the experiments are in every sense parallel (Fig. 8).

The observations made on Dog E 130, with a pancreatic fistula, show that even if an animal loses over half the amount of pancreatic juice secreted and yet maintains a stationary body weight there is no loss in the size of the spleen.

Data were collected on dogs with pancreatic fistulas complicated by infection in order to study the effects of pancreatitis on the spleen, since Sweet has suggested that in this direction may be the explanation of the anemia of pancreatitis found in certain cases by Musser. Save for a more acute and marked loss in weight of the animals, caused doubtless by the toxemia of the infection and by the dehydration and loss of alkali resulting from the constant secretion of large quantities of juice from the fistula, the results obtained in these cases seem entirely comparable with those obtained in the cases of fasting and removal of the external secretion of the pancreas.

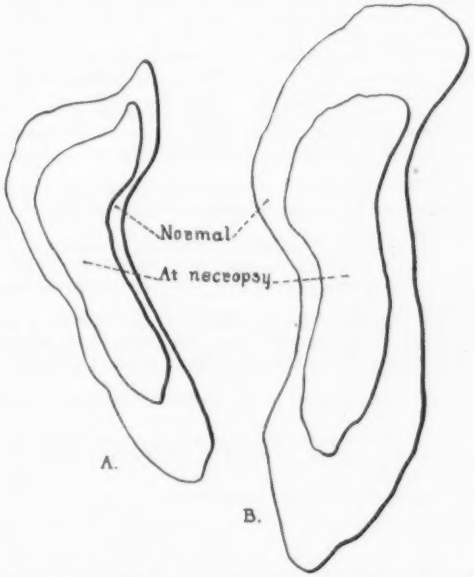

FIG. 8.—Marked shrinkage of the spleen. *A*, in fasting (D 875); *B*, following partial pancreatectomy with loss of external secretion of pancreas (D 661).

It might be expected that in acute infections, for example, the cases of acute pancreatitis, of distemper, and of peritonitis, given in the protocols the toxemia would cause enlargement of the spleen in the form of acute splenic tumor. Yet in these infections the animals refuse food and assimilate poorly what is taken. Marked loss of weight develops and, as shown in these experiments, the spleen diminishes in size.

Of what significance is this extraordinary atrophy of the spleen in inanition? Why must this organ, next to the inert tissue, fat, give so readily and lavishly of its substance for the nourishment of its host? Does such lavishness imply that this unique gland

can play but a slightly important part in the general economy and physiology of the organism; or may it still be that the spleen can give heavily of its substance in famine and yet remain a valuable organ with divers and sundry useful though little known functions? Or does the spleen with specific purpose aid in the garnering and temporary storing of protein food materials in order that it may dole out sustenance when the body is hard put?

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GASTROSPASM: A CLINICAL AND ROENTGENOLOGICAL STUDY.[1]

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Even before the roentgen-ray era local gastrospasm, especially such that occurs at the entrance and exit of the stomach (cardio-

[1] Read in part by J. Roemer, M.D., at the annual meeting of the New Jersey State Medical Society, June 15, 1920.

and pylorospasm respectively), was clinically known. In 1881 Strumpell called attention to what he named esophagismus, describing the spindle-shaped dilatation of the esophagus, and Mikulicz demonstrated it by his esophagoscope. Spastic pylorospasm in the adult was first described by Kussmaul and in the infant by Still. Complete gastrospasm was mentioned by anatomists and physiologists (Home, Tiederman and Gmelin) in the early part of the nineteenth century. Local segmentation of the stomach was mentioned by Retzius, who found it at the autopsy of a man who died suddenly during the stage of digestion.

Williams described the human stomach to possess three natural physiological constrictions: (1) Near the cardia which corresponds to the incisura cardica (His); (2) in the middle of the stomach; (3) at the antrum. Banchi, Cunningham and Orr mentioned the physiological pseudo-hourglass constrictions. Buedinger found during a laparotomy a spastic hourglass opposite the seat of the ulcer. Simmonds found at autopsy an hour-glass stomach with no demonstrable lesion in any part of the stomach. Becky injected the human stomach, soon after death, with formol and often found contraction phenomena corresponding to an hourglass. Recently, Waldvogel[2] demonstrated by inflation of the stomach that gastrospasm is not an infrequent occurrence.

Whereas this historical introduction serves to show that the subject is not new, we must not lose sight of the fact that its clinical importance and the possibility of diagnosing it correctly are the achievements of the roentgen-ray study by means of the contrast meal. It must be emphasized that gastrospasm as a sign is demonstrated by the roentgen-ray, but its diagnostic significance can only be interpreted by a complete clinical study.

Gastrospasm was aptly divided by Holzknecht and Luger[3] into regional, circumscribed and total. Regional gastrospasm may occur in any part of the stomach; the most common locations are at the cardia and pylorus.

Cardiospasm. Although cardiospasm primarily belongs to the cardiac end of the esophagus, its relation to gastric diseases and its symptomatology are so purely gastric that brief mention of it must be made here. We understand by cardiospasm a spastic contraction of the cardiac end of the esophagus, of shorter or longer duration, sometimes lasting for weeks and even months and leading to dilatation above the contraction. From an etiological standpoint cardiospasm is in the great majority of cases purely functional. This is easily understood when we recall that the propulsion of food from the esophagus into the stomach is mostly controlled by the autonomic nervous system. That is why the esophagus can be entirely stripped of its musculature if the mylohyoid muscle remains and

[2] München. med. Wchnschr., 1911, No. 2.
[3] Mitteilungen auf dem Grenzgeb., 1913, p. 669.

the nerves be intact, without disturbing the passage of food from the esophagus to the stomach.

This is not the place to enter into a detailed discussion of the physiology of deglutition and of the epoch-making and conclusive experimental work of Kroenecker, Meltzer, Cannon, Krauss and others; but some mention must be made of the innervation of the lower end of the esophagus and cardia.

The chief nerve supply of the motor function of the lower end of the esophagus and cardia is derived from the vagus. The influence of the sympathetic nerve fibers on the lower end of the esophagus is today also conceded. The existence, however, of intrinsic nerves of the lower esophagus and cardia able to carry out the function independent of whether or not the chief nerve supply is intact was demonstrated by Cannon. These nerves are important when they are called upon to take up the expulsion of the food from the lower part of the esophagus to the stomach and when there is obstruction at the cardia on account of an organic disease of the vagus. We thus see the important role played by the vagus and its allied nerves in controlling the act of deglutition. The disturbance of deglutition due to organic affection of the vagus and its allied nerves, either centrally or peripherally, is well known, but functional diseases of the vagus may also bring about disturbances in the act of deglutition either by derangement of the vagus directly supplying the esophagus or by way of reflex. Reflex disturbances need not originate in the vagus; they may also originate in the sympathetic system. It is therefore reasonable to assume that cardiospasm is primarily an outcome of irritability of the vagus. The underlying factors bringing about such a state have been divided by Held and Gross,[4] into five groups.

In the first group are the patients whose vegetative nervous system is below par through inheritance. Almost throughout their lives they have some physical disturbance brought about by an unstable vagus or sympatheticus, and are also subject to cardiospasm. Although physically perfectly healthy, such people are found to have objective signs of vagotonia or sympathicotonia or the two mixed, and in the history we will hear that from childhood almost all organs supplied by the vegetative nervous system have at one time or another been subject to a functional disorder (enuresis nocturna, periodical vomiting, laryngospasm, urticaria, etc.).

To the second group belong the cases in which the vegetative nervous system becomes involved because of an inborn status asthenicus or status thymicolymphaticus. It is true that the status just named not rarely presents an inborn instability of the vegetative nervous system, but in a considerable number of cases we have found that the disturbance in the various organs brought on by

[4] Jour. Am. Med. Assn., June 22, 1916.

hyperirritability of the vagus and sympathicus is secondary. These individuals are not equal to the task of great responsibilities, either physically or mentally, and when overtaxed they need not necessarily acquire organic diseases, but they become subject to functional derangement of the vegetative nervous system. This may manifest itself in any of the organs supplied by the vegetative nervous system, and with equal frequency in the esophagus, causing cardiospasm. In this group belong the cases of gastroptosis, especially "long stomach" (langmagen), in which traction on the esophagus is the causative factor (Rovsing). Here also belong cases of cardiospasm resulting from sudden psychical trauma in individuals previously apparently healthy.

The third group contains the cases which show cardiospasm due to reflex irritation from other diseased organs (ulcus ventriculi, carcinoma of the fundus and lesser curvature, gall-stones, kidney-stones, diseases of the generative and genito-urinary organs, pancreatitis chronica or left-sided diaphragmatic pleurisy). Here, too, the underlying disturbed vegetative nervous system is a predisposing agent.

In the fourth group belong the cases of cardiospasm due to infections by toxic and metabolic agents (nicotin, lead, uremia, parasites, gout, chorea and lyssa).

In the final group belong the cases in which a local esophageal disease is the causative factor (fissure, erosions, scar-tissue formation and ulcus pepticum esophagi).

Symptomatology. It is important to know that the onset of cardiospasm is sudden and the first attacks may be of a short duration. Its transiency is best illustrated by two cases observed by us, one of a woman, who after a sudden shock by grief immediately developed cardiospasm which lasted several hours and recurred three weeks later. Another case is that of a man who presented clinical symptoms of cardiospasm which lasted three months. During fluoroscopic examination for half an hour the esophagus presented a characteristic sausage-shaped dilatation. Upon the administration of a Seidlitz powder, which was given merely as a suggestive measure, the spasm suddenly relaxed. These cases are cited to emphasize how frequently the affection is purely functional. In the majority of cases, however, once symptoms set in persistence is the rule. The severity of the symptoms varies, sometimes the patient can swallow solid food and no liquids, and at other times they can swallow liquids easier than solids. The severity of the symptoms depends greatly on the underlying causes. Often the patient will state that the first few morsels of food stop at the cardia and relief is experienced by taking more food; he even feels it going down into the stomach. When the condition persists, food stagnates in the esophagus, causing epigastric distress, substernal pressure, pain in the chest and belching and regurgitation of decomposed

food. There are often salivation and fetor *ex oris*. When extreme dilatation takes place the patient may have the false belief of feeling better, for he can partake of a larger meal. But if he takes a little more and reclines after it the food is regurgitated unchanged. Some patients vomit large quantities of food taken days before, simulating pyloric stenosis. This often leads to emaciation. In advanced cases the food is regurgitated in a state of fermentation and decomposition, showing the presence of lactic acid, butyric acid and sugar. In such cases due to these organic acids the patient has a continuous substernal burning. Pain as a symptom depends entirely upon whether the sensory nerves are co-affected or not. If so the pain is out of proportion to the disease and an attempt to swallow a little cold water causes severe pain in the region of the ensiform process, radiating to the soft palate, uvula, epiglottis, left side of the chest and sometimes both sides. Such pain is especially common if the spasm is due to a fissure at the cardia. A patient with cardiospasm observed by us was particularly troubled by pain as described above. Her blood showed a four-plus Wassermann and we hoped that antiluetic treatment might prove effective, which, however, was not the case. This made us doubt whether the existing lues was the underlying cause. Whereas the symptoms just described are typical of cardiospasm, very indefinite complaints such as feeling a fulness immediately after the smallest meal, belching and pressure in the epigastrium should lead us to examine carefully for a minor degree or cardiospasm. This is especially found in individuals of status asthenicus with a very long stomach in whom traction on the esophagus by the long stomach is supposed to cause spasm. To us it seems more plausible that the spasm is brought about by an undermined vegetative nervous system.

The physical examination should be directed not only toward establishing the disease, but also, if possible, to determine the cause; and therefore we should look for such clinical manifestations which indicate instability of the vegetative nervous system, *i. e.*, the vagotonic complex (Eppinger and Hess), such as dilatation of the pupils, slow pulse, slowing of the pulse when pressing on the eyeballs (Achner phenomenon), slowing of the pulse in bending forward, dry skin and pallor and spastic constipation. Not all symptoms must be present to complete the picture, and in reality some of the organs may show manifestations of sympathicotonia. Of course, it cannot be emphasized too strongly that the finding of symptoms of an unstable vegetative nervous system does not exclude organic disease. In fact it is to the credit of von Bergmann and his pupils, who demonstrated that such state predisposes to ulcer of the stomach and duodenum. It is surely of clinical importance to recognize the fact that in an organic disease like gall-stones or renal colic, if associated with cardiospasm, vagotonia plays quite a role as a predisposing causative factor.

Sounding. A soft stomach tube, not less than 10 mm. in width, should be used. In cases of spasm one has the sensation as if the tube were tightly held by the spastic esophagus. Sometimes sudden relaxation takes place and one feels the tube sliding down. The above-described sensation is more pronounced when a solid sound is introduced. The obstruction to the passage of the sound is not constant. Antispasmodics employed for a few days in the form of tincture belladonna, 10 minims, three times a day, or atropin, $\frac{1}{100}$ grain, two or three times a day, or papaverin, $\frac{1}{6}$ grain, three times a day for a few days, or benzyl-benzoate, 30 minims, three times a day, or making the patient drink some oil before the sound is introduced, may relieve the spasm.

Esophagoscopy. Most of the observers who use the esophagoscope with skill, such as Yankauer and Janeway, state that no definite information is obtained by this method. Both Rosenheim and Stark state that in certain cases hyperemia and in other cases ischemia were seen above the spasm, and also folds enclosing a narrow half-moon slit or even a pin-point opening above the spasm.

FIG. 1

Roentgen-ray Diagnosis of Cardiospasm. A most important radioscopic and roentgenographic sign is the visualized active peristalsis above the seat of the spasm. This is more marked in early and transient cases than in the advanced cases in which dilatation above the obstruction is very pronounced. The reason for that lies in the fact that the more the obstruction is due to spasm the more the

entire esophagus is in a state of hypertonus, and with its strong musculature tries to overcome the obstruction. In cases of obstruction at the cardia which result from idiopathic dilatation, where atony of the esophagus musculature is a primary factor, there is no peristaisis. Peristalsis of the esophagus is likewise absent in most of the cases of carcinoma at the cardia because of the associated loss of tone of the esophagus musculature. We differentiate two kinds of spasm: incomplete and complete. The former manifests itself fluoroscopically and roentgenographically as follows: The contrast substance is seen to hold at the point of obstruction and the esophagus above fills in an irregular spindle-shaped form exceeding its normal width two- or threefold. For a few moments nothing may be seen to pass through the obstruction. Repeated empty swallowing often overcomes the spasm. In the latter a uniform dilatation with visible contraction is seen above the obstruction. Through the obstructed area nothing may pass or a very thin streak of the contrast meal. If the condition persists for a very long time, dilatation may be so advanced as to permit the esophagus to hold from 200 to 300 cc of fluid. We can then see fluid in the dilated esophagus even without contrast substance. The esophagus looks sausage-shaped (Fig. 1), but shows peristalsis. The presence of peristalsis serves to differentiate cardiospasm from idiopathic dilatation or dilatation due to obstruction by cancer.

Rumination (Incomplete Cardiospasm). It seems of interest to us to record in this connection a case of rumination we had occasion to observe. While the patient swallowed the contrast meal which after a few morsels was seen to pass into the stomach with ease, the lower half of the esophagus would suddenly dilate and the patient would feel the food come back into the mouth. The patient would rechew it and swallow it again, then the food would suddenly drop into the stomach. This fluoroscopic study was an excellent demonstration of Meltzer's physiological studies as to the act of deglutition, *i. e.*, that the closure at the mouth of the esophagus during swallowing brings about the opening of the cardia (Figs. 2 and 3). Fig. 2 was taken immediately after the contrast substance was swallowed and Fig. 3 was taken one minute after the patient was asked to swallow empty. While fluoroscoping the patient during the act of deglutition we asked him to give a signal the instant he felt the food pass back into the mouth. The signal corresponded exactly to the time when the spasm in the cardia set in. This observation gave us a hint to advise the patient, instead of ruminating, to reswallow as soon as he felt the food back in the mouth or at the first sensation of distress in the epigastrium. Since then the patient reported repeatedly considerable improvement but not cured. Another illustration of how disturbance in the region of the mouth of the esophagus produces reflexly cardiospasm is demonstrated by a case of Zenker's diverticulum as shown in Figs.

FIG. 2

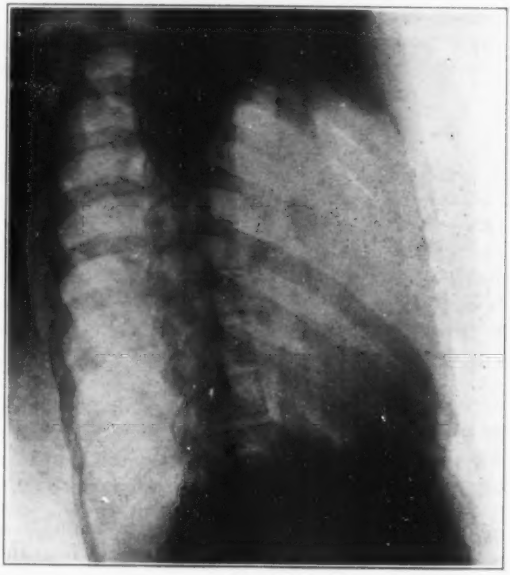

FIG. 3

4 and 5. (Fig. 4 shows the diverticulum and Fig. 5 the spasm.) Another case worth mentioning in which cardiospasm was caused

FIG 4

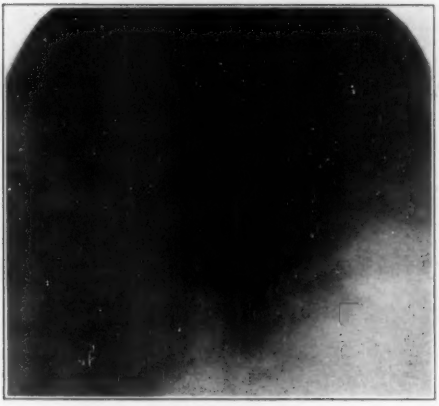

FIG. 5

by pressure in the upper part of the esophagus was due to an aortic aneurysm. It is interesting that these patients in whom the cardiospasm is brought about by disturbance in the upper part of the

esophagus, either as a result of disturbance of innervation (the case of rumination quoted above or anatomical defect, as in the case of Zenker's diverticulum, or if due to pressure from without, as in the case of aortic aneurysm) complain that the food stops in the throat or in the upper part of the esophagus.

Regional Spasm of the Stomach. Approaching the stomach proper the most frequent seat of regional spasm is that of the pylorus, so-called pylorospasm. Pylorospasm is a condition in which a part or the entire pylorus is in a spastic state for a shorter or longer duration. When a spasm persists for a long time it may even lead to hypertrophy and marked thickening of the pylorus with a resulting palpable mass simulating a tumor.

ETIOLOGY. Pylorospasm may be caused by intra- and extragastric disease (intrinsic and extrinsic—Carman). The intragastric cause is by far the less frequent, and if present is mostly the outcome of a prepyloric ulcer less frequently due to ulcer on the lesser curvature of the stomach and still less frequently in duodenal ulcer. We have seen it occur in gastro-enterostomized patients. Like Carman and Miller we saw it occasionally in carcinoma of the stomach.

The extragastric causes for spasm are numerous. According to our experience gall-bladder disease heads the list. Holzknecht and Luger were the first to call attention to the frequency of pylorospasm in gall-bladder disease, and they pointed out that the existence of a solitary stone in the gall-bladder is more prone to give rise to such spasms than multiple stones. Their observations were since then confirmed by Carman, Case and others. Our experience as demonstrated by Fig. 6 fully confirms their views. Other causes are chronic pancreatitis, chronic appendicitis, renal calculi, chronic lead-poisoning, morphine-poisoning, tabes dorsalis and chronic interstitial nephritis, particularly during the stages of suburemia and uremia.

SYMPTOMS. These, of course, vary, depending on the underlying cause. Where an intragastric cause like ulcer or cancer is responsible the well-known symptoms are present, which need no discussion. We consider it of sufficient importance to dwell more or less fully on the discussion of pylorospasm produced by gall-bladder disease, particularly gall-stones. Such individuals, independent of gall-stone colic, or even in the absence of any acute attack, have a long and persistent row of vague gastric symptoms. They complain almost continually of fulness in the upper quadrant of the abdomen. Just as soon as they begin to eat they feel that they have to stop because of pressure in the epigastric region, which is often relieved by spontaneous or forced belching. They often complain of pain of varying severity relieved by the application of heat. Such slight attacks generally occur during eating. Mental and physical exertions have a more deleterious effect than dietetic errors. The

tendency for these symptoms is to persist and eventually to lead to emaciation and pallor, and in extreme cases almost resembling carcinoma of the stomach. These symptoms, vague as they are, in the absence of definite physical findings, are often attributed to neurosis, and, in a sense, they are neurotic and functional in nature. These patients in the majority of cases have an unbalanced autonomic nervous system. By physical examination alone, no matter how painstaking it may be, it is very difficult to establish a diagnosis. Even the best palpation, including the Housman deep-sliding method of the pylorus, will seldom determine the existence of a spastic pylorus. In the pre-roentgen-ray era experts on palpation claimed to have succeeded in palpating a spastic pylorus.

FIG. 6

Experts, however, are the exception. The roentgen-ray, on the other hand, makes us visualize spasm with ease and offers an explanation for the symptoms.

The roentgen-ray findings are as follows: Fluoroscopically the food is seen to stop at the antrum, and sometimes even for several minutes no food at all is seen to pass, and what enters the pylorus appears in the form of a narrow canal or pivot-shaped. Palpation does not change the contour of the pylorus. The roentgen-ray plate (Fig. 7) shows the above-described phenomenon. The stomach proximal to the contracted pylorus shows dilatation and active peristalsis. It was already stated above that the clinical and roentgen-ray manifestations are such that to distinguish between these and carcinoma becomes very difficult. We may state that we, like others, had cases of persistent pylorospasm with anacidity.

These we submitted to operation with a doubtful diagnosis, but inclined to carcinoma. In 2 cases the pylorus was so hard and thick that the surgeon had to open the pylorus to convince himself that there was no tumor within. One of the cases was operated by Dr. Richard Lewisohn and the other by Dr. A. A. Berg. In cases in which the hypertrophied pylorus gives rise to a palpable mass and the contrast meal fails to fill the pylorus the differential diagnosis between spasm and cancer is almost impossible.

Regional spasm may occur in the fornix or tube of the stomach. In these cases it is brought about by pressure from without. We observed a patient in whom a large spleen made the upper part of the stomach from airbag to midpart of the tube appear like a narrow rigid canal with no peristalsis and a very small and deformed

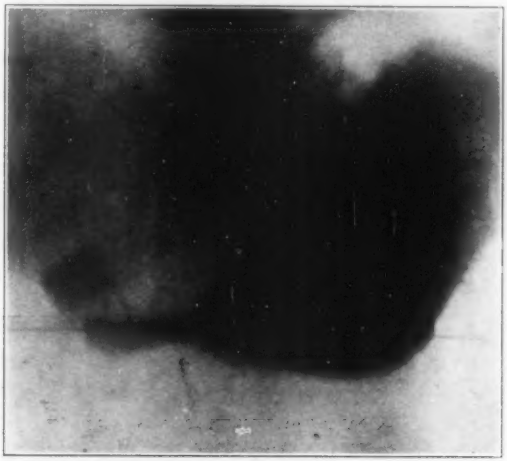

FIG. 7

air-bag. The palpable mass of the left side, which was the enlarged spleen, awakened the suspicion that the tumor might have been due to a malignant disease of the stomach. Inflation of the colon with air made the outline of the spleen to the palpating hand more definite A more extensive spasm of the stomach, taking in the tube and pylorus and making the cardiac end appear funnel-shaped, was seen by us in a woman with a large fibroid tumor of the uterus. A similar spasm of the fornix and part of the tube was seen by us in a case which at the laparotomy performed by Dr. William Spickers disclosed tuberculous peritonitis with tubercles scattered over the serosa of the stomach (Fig. 8).

Regional spasm of the tube or pars media, with dilatation of the cardiac end and the pylorus, is sometimes encountered. It is usually

of extragastric origin and only the clinical history can establish the cause.

A frequent seat of regional spasm is encountered in the stomach just below the incisura cardiaca. We do not refer to the standing

Fig. 8

Fig. 9

contraction or the incisura on the greater curvature. This is to be discussed below. What we have reference to here is, as shown in Fig. 9, that the contrast substance is held at the point mentioned above. The fornix is seen dilated and sometimes from five to ten minutes either no food is seen to come down or only a thin streak

of contrast substance along the lesser curvature. In the former case the fornix presents a pear-shaped or triangular appearance (Fig. 10); in the latter case the narrowing below the dilatation bears resemblance to a cardiospasm with the dilated esophagus above it. We have therefore conceived the idea that the spasm is not only local, but that it involves the greater part of the tube. We were led to this observation accidentally, viz., through a patient who complained of severe choking sensation, pressure and fulness in the epigastrium after meals. The symptoms were at times so annoying that he would have to stop, when on the street, at any physician's office for the purpose of obtaining relief, for he feared lest he might choke. Nose and throat examination by specialists was pronounced

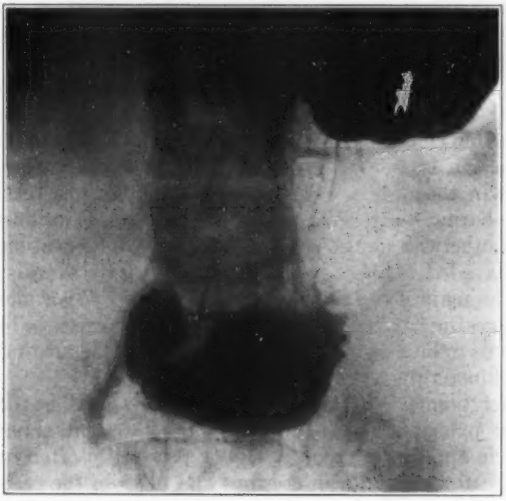

FIG. 10

negative. We studied his esophagus fluoroscopically with a contrast emulsion, as advocated by I. S. Hirsch, in order to exclude obstruction or a diverticulum of the esophagus. The esophagus was found to be normal, but as the emulsion entered the fornix it filled out that part and no particle of the contrast substance was seen to enter the tube. Massage of the fornix could not press the food down. Only after a few minutes a thin streak was seen to dribble down along the lesser curvature. It appeared to us as if we were dealing with an organic hourglass contraction. We then gave him the ordinary barium-buttermilk meal and the stomach filled completely. We had the patient return two days later after the administration of belladonna (according to the method of Carman) and repeated

the examination as before, and observed the same phenomena. A few days after the second examination we examined him again with the ordinary barium-buttermilk meal, when this phenomenon was entirely absent. When we then questioned the patient a little more in detail about his gastric symptoms most of his complaints, clinically, suggested gastric ulcer. The chemical analysis of the stomach contents showed marked hyperacidity. We placed the patient on a Sippy treatment, with gratifying results.

We were at once impressed by the thought whether the spasm below the fornix, just at the junction of the fornix with the tube, may not give rise to symptoms of spasm in the upper part of the esophagus similar to cardiospasm. We also reasoned that where there is an irritated area at a certain point in the stomach a meal that would tax that part of the stomach more than the buttermilk meal may demonstrate the functional disturbance brought about by such irritation.

We have since then adopted the procedure to start all our gastrointestinal roentgen-ray examinations with a few tablespoonfuls of the barium emulsion. We may state now definitely that normally this emulsion is seen to pass down the lesser curvature without stopping in the fornix. This emulsion fills out the fornix better than the barium-buttermilk mixture, and therefore outlines it when it would otherwise not be seen. Thus far our observations of such spasms have led us to believe that the cause for the same is intrinsic, and in the majority of cases is most likely due to an ulcer on the lesser curvature at the point where the ulcer exists. The spasm seems to us to be a protective phenomenon, analogous to the spasm in the sphincter pylori in cases of pyloric ulcer.

Another point of very frequent regional spasm is that of the sphincter pylori. This condition is often brought about reflexly by chronic appendicitis, colicomucosa and is also often functional. It has great significance in erosions and ulcer in the region of the sphincter pylori. Such erosions may give rise to periodical gastralgia, terminating in vomiting large quantities of fluid, but rarely solid food. Vomiting gives great relief; morphine, on the other hand, may make the condition worse. If the condition lasts a long time, dilatation and hypertrophy of the pylorus become so marked as to give rise to a palpable tumor. Schnitzler[5] reported a case in which a tumor the size of an orange was felt in the epigastrium. That patient was operated. At first the surgeon did not find any evidence of a tumor, but while palpating the pylorus the tumor reappeared. A similar case was observed by us. Schnitzler considers an erosion in the sphincter pylori analogous to an erosion in the sphincter ani, and advises pyloroplasty in such cases.

The fluoroscopic and roentgenographic appearance in such cases is most striking, as shown in Fig. 11. The pylorus appears as if

[5] Wien. med. Wchnschr., 1891.

suddenly cut off and is immensely dilated. Forcing the food out while fluoroscoping we see only a narrow stream of contrast substance which fills the first portion of the duodenum very thinly, giving it the appearance of a goose feather. Sometimes we may watch for several minutes without seeing any food going through the pylorus. If we fluoroscope and make plates of such cases an hour or two after the ingestion of the contrast meal very little is seen to have left the stomach. If the spasm is of extragastric origin it is usually very transient and there is only a very moderate delay in the emptying of the stomach, and, as a rule, no six-hour residue is present. If there be a large six-hour residue in such cases we usually find the rest of the contrast substance in the terminal ileum, which is considerably dilated. The cecum, as a rule, contains very

FIG. 11

little or no contrast substance at all. This seems to us to indicate the existence of a spasm in the sphincter of the ileocecal valve, and that is most likely the primary cause of the spasm in the sphincter pylori. The delay in the emptying of the stomach may not depend entirely on the persistence of the spasm in the sphincter pylori, but to a great extent upon the fact that the small intestines are filled, and therefore the so-called intestinal hunger (Pawlow) is not present.

When the spasm of the sphincter pylori is due to a local erosion the six-hour residue is large, the terminal ileum containing little contrast substance, or may be entirely empty, and the distribution through the colon may not be normal. The reason that the small intestine contains so little contrast substance, although the stomach

contains much, is explained by the fact that the food is so thoroughly liquefied in the stomach that it runs through the small intestines rapidly.

Incisura. The incisura or spastic hourglass has been made accessible of recognition by means of the roentgen-ray. It appears mostly on the greater curvature, a little below the incisura cardiaca. It may, however, appear in any other part of the greater curvature of the stomach. It may be transient or persistent. There is, usually, one incisura, but two or three may be present. The depth and width of the incisuræ vary from that of a small nick to a deep indentation reaching the lesser curvature and giving the stomach a bilocular appearance (Fig. 12). Where there are two or three incisuræ the

FIG. 12

stomach appears as if it were divided into several compartments. These incisuræ may be of extra- or intragastric origin. Such incisuræ are met with occasionally in cases of chronic appendicitis and gall-stones. Very rarely they appear spontaneously in such cases during fluoroscopic examination, but more commonly, as pointed out by both Case and Carman in this country and Borsany and Hurst abroad, such incisuræ are brought about when pressure is exerted over the diseased organ (appendix, gall-bladder and duodenum) while fluoroscoping. Even under such circumstances it is not a common occurrence. It has been our experience that when pressure on the diseased appendix or gall-bladder brings about such indentation it is very transient and lasts only as long as the pressure is continued. More commonly it is seen in neuropathic individuals,

especially when vagotonia is predominant. Also, pressure from without, such as a tumor in the left hypochondrium, a large spleen or even gas in the splenic flexure, may produce such spasm. The most important intragastric cause for spasm is an ulcer on the lesser curvature of the stomach opposite the incisura (Fig. 13). The spastic incisura, whether or extra- or intragastric origin, may be transient and disappear spontaneously while fluoroscoping or may persist during one examination and be present at the next examination. Deep and wide incisuræ, situated opposite an indurated or penetrated ulcer on the lesser curvature, are usually persistent and only disappear under deep narcosis. That is why the surgeon in the early days of roentgen-ray diagnosis contradicted the roentgen-ray

FIG. 13

findings of an hourglass. The differential diagnosis between spastic incisuræ of extragastric origin and that due to ulcer on the lesser curvature of the stomach is made by the administration of antispasmodics like atropin or tincture of belladonna, according to the method of Carman, or papaverin or atropapaverin, as advocated by Holzknecht and Skolitzer.[6] The disappearance of the incisuræ after antispasmodics, according to our opinion, does not exclude an ulcer on the lesser curvature. The persistence of the incisuræ, on the other hand, especially if a niche is seen on the lesser curvature, establishes the diagnosis of ulcer with absolute certainty.

A rare type of incisura occurs on the lesser curvature just below the air-bag, indicating the seat of an ulcer. A case with such incis-

[6] Wien. klin. Wchnschr., 1913, No. 26.

ura observed by us showed at operation no ulcer but a large solitary stone in the gall-bladder. Another rare form of incisura is mentioned by Faulhaber, from whose monograph Fig. 14 is taken. In this type the cardia is to the left and is accompanied by a narrow isthmus to the rest of the stomach which lies to the right. Primarily, Faulhaber correctly interpreted this as being due to an ulcer on the lesser curvature or to adhesions of the posterior wall of the stomach to the pancreas. Recently a number of publications appeared in foreign literature, notably among which are those of Rieder, Zehbe[7] and E. Schlesinger.[8] Rieder named this form of a stomach a cascade or waterfall stomach (Fig. 14). This form of a stomach presents a standing contraction or incisura on the greater

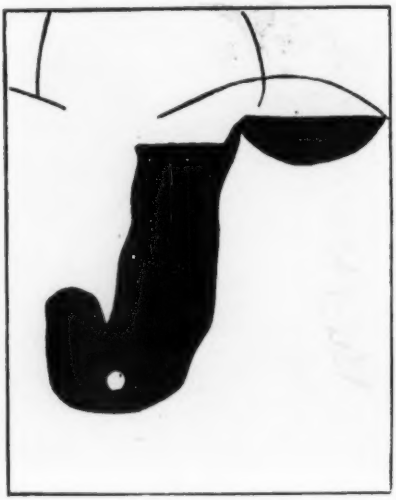

FIG. 14.

curvature just below the cardia, but instead of the corpus and pylorus running in the vertical axis the corpus and pylorus in the cascade stomach adopt the sandal or bull-horn shape. It seems justifiable to assume that such a stomach presents evidence of regional and partial gastrospasm combined. The regional spasm is demonstrated by the incisura and the partial by the narrow transversely situated tube and pylorus. That this condition is purely spastic is evidenced by the fact that it is not persistent and that it frequently disappears after the use of antispasmodics. Both intra- and extragastric disease play a role in the etiology of this condition.

[7] Fortsch. auf dem Grentz., Roentgen Strahlen, vol. xxv, p. 107.
[8] Ibid., vol. xxvii, p. 261.

It is a striking fact, which was observed by E. Schlesinger and confirmed by others, that duodenal ulcer frequently brings about such spasm. Fig. 15 shows a duodenal ulcer in a cascade stomach observed by us. Such condition can also be brought about by gas distention of the descending colon, a large spleen or tumors in the left hyperchondrium. In such a stomach the cardia or fornix is dilated, the air-bag is broad and presses against the left dome of the diaphragm with resulting clinical symptoms brought about from such pressure. This may also explain the frequent occurrence of left-sided pain in the duodenal ulcer. The organic hourglass of the

FIG. 15.

stomach due to ulcer, cancer and syphilis of the stomach will not be discussed here, as it does not belong to our subject. Before leaving the subject of incisuræ it seems in place to call attention to the fact that the phenomenon was much more frequently seen in the early days of gastro-intestinal roentgen-ray studies than now. This question has confronted us, and we thought that the reason for it may be in the difference of the consistency of the contrast meal. In the early days when a semisolid carbohydrate meal of Rieder was used the quality and consistency of the meal was of a nature to tax the perisystole in the fornix and upper part of the tube unless the stomach was very markedly hypotonic or atonic. A carbo-

hydrate meal remains longer in the fornix because salivary digestion continues there for a few minutes. The spastic incisura on the greater curvature has been considered as a protective phenomenon to prevent the food from irritating the ulcer-bearing area.[9] When a light fluid meal like the barium-buttermilk meal is given the meal is not sufficiently irritating to call upon such protective phenomena. A further proof that the lack of the filling of the fornix is responsible for the rarity of the incisura is furnished by the fact that when the fornix is made to fill by postural changes, such as having the patient lie on his back and obliquely (Levy-Dorn), an incisura may be brought out when it would not otherwise be seen. This cannot be due to local pressure from without because that position serves to evade pressure. We have therefore adopted the procedure to study all our cases in the Levy-Dorn position, with the barium emulsion as described above. If after such examination a conclusion is not reached the patient should be reëxamined with a Rieder meal. The reason we do not start the Rieder meal at first is because the fluid meal is better adapted for the study of the first portion of the duodenum and the appendix.

Total Gastrospasm. Total gastrospasm is the rarest of all forms of spasm and is in most cases of extragastric origin. Cases reported in the literature were due to chronic lead-poisoning, tabes dorsalis and morphinism. A case was seen by us in which the stomach looked like a narrow tube without any peristalsis and a gaping pylorus, and which we diagnosed as scirrhous cancer. This patient was operated by Dr. T. A. Dingman and no lesion was found in the stomach, but the appendix showed evidence of chronic inflammation. A case is mentioned in the literature which was due to gallstone disease. Carman reported a case of gastrospasm produced by a small cancer on the lesser curvature of the stomach. Gastrospasm is characterized by an extreme hypertonus. The stomach is considerably diminished in size. It is situated very high in the abdomen, most of it to the left of the median line. The air-bag is small, peristalsis is almost absent and the food is seen to pass continuously into the small intestine. It resembles almost entirely a scirrhous cancer. The resemblance of all forms of gastrospasm to filling defects due to cancer is so striking that rightfully does Carman make the statement that not only is the novice in danger of mistaking it for cancer, but the expert as well.

[9] Held and Gross: Am. Jour. Med. Sc., May, 1918.

THE BEST TECHNIC FOR GASTROENTEROSTOMY AS DETERMINED BY FUNCTIONAL RESULTS.

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For a number of years the operation of gastroenterostomy has been gradually losing in favor, and at the present time dissatisfaction with this surgical procedure is approaching an extreme point. It has therefore seemed to be of value to summarize observations made on patients subjected to this operation with the object of demonstrating the accompanying and resulting phenomena; these seem to explain amply the reasons for this dissatisfaction. And inasmuch as the making of a gastroenteric anastomosis is on occasion a necessity, the observations have further value in enabling a selection of the best type of technic for this purpose. It seemed best to utilize only the clinical notes and observations of patients actually afflicted with ulcerative conditions; animal work did not seem appropriate, since none of the ordinary laboratory animals are naturally susceptible to this disease.

The methods employed in making these studies depends upon the estimations of the functional capacity of the stomach and were fully described on a previous occasion. Inasmuch as gastroenterostomy is most frequently made for chronic ulcerations of the stomach or duodenum, none other than these ulcer cases, except for the control cases, are included in the report. The patients upon whom these studies were made were not selected in any way and the studies were made *seriatim* as the patients were consecutively admitted and discharged.

The necessary control observations were made by selecting a number of patients in whom at exploratory operations it was definitely established that no pathologic lesion existed in the stomach or duodenum. The observations made in these cases before and after operation showed close similarities. The facts of these observations are summarized in Table I and Fig. 1. In detail these are:

TABLE I.

MOTOR FUNCTION.

Case.	Roentgen-ray.		
	Tone.	Peristalsis.	Empty in.
1	Good	Active	4 hours.
3	Good	Active	4 hours.
4	Good	Active	6 hours.
2	Fair	Fair	6 hours.
6	Good	Active	6 hours.
7	Good	Active	6 hours.

CHEMISM.

Case.	Fasting contents; residue in cc.	Ewald test-breakfast.			Riegel test-meal; residue in cc.
		Residue in cc.	Free acid.	Total acid.	
1	0	40	35	65	0
3	0	100	50	75	0
4	0	60	..	..	0
2	0	75	35	75	0
6	0	50	60	80	0
7	0	35	30	60	0

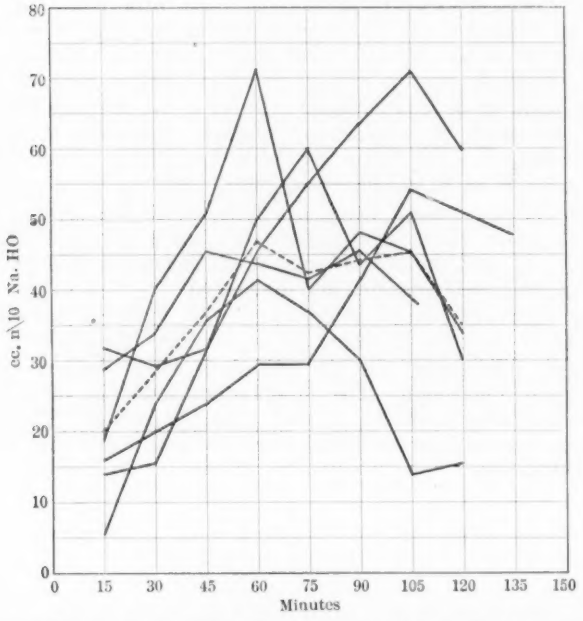

FIG. 1.—Fractional test meal. Specimens extracted until the stomach is empty. Estimations in terms of cubic centimeters of decinormal sodium hydrate solution. The dotted line represents the average of all the curves in the figure. These facts apply to Figs. 2, 3 and 4 also.

1. There is no fasting contents in the stomach or, at most, it consists of a few cubic centimeters. The latter is mostly mucus, more rarely a thin watery fluid, and very rarely is bile-tinged. It usually contains no or very little free hydrochloric acid and a low total acidity. Frequently there is no acid content.

2. After an oatmeal gruel test meal hydrochloric acid is secreted rapidly and the total concentration rises and reaches its maximum approximately sixty minutes after ingestion. Thereafter the total concentration tends to fall and approach the level from which it began.

3. The secretion of digestive enzymes is constant and the latter can always be demonstrated in abundance.

4. Depending on the character and quantity of food the stomach is emptied after a certain time and afterward the stomach contents resemble the original fasting contents. With carbohydrate meals the average emptying time is from two to three hours; with protein meals, six hours or more.

5. The motor activity of the stomach wall is normal. The roentgen-ray demonstrates that peristalsis is active and efficient; with the barium zoölak contrast meal the stomach is seen to be empty within six hours.

These are the salient characteristics of normal stomachs.

The biologic history of chronic ulcer of the stomach or duodenum includes definite manifestations of disturbances in the normal physiologic activities. In previous studies these were all severally considered. It was possible to demonstrate that functional disturbances were not always present to any considerable degree and that there was no elicitable relationship between the situation of the lesion, its size or structural characteristics, or of any anatomic complication, and the character and intensity of the physiologic changes and of the subjective symptomatology. Without going into any detailed description of these relative factors the progression of the illness is, in the large majority of cases, accompanied by a progressive increase in the functional disturbance; this is especially marked in the motor aspects.

There are several ways of making a gastroenteric anastomosis and the procedure may be added to by creating an artificial blocking to the passage of the stomach contents through its normal outlet (unilateral pyloric exclusion). The operation usually done follows the method of von Hacker, and the anastomosis is made either by suture or by the Murphy button, depending on the ease with which either could be done or on the exigencies of the individual case; preference has always been given to the suture method. With the suture method the stoma is made large enough to easily admit two fingers, and is given a vertical application to the posterior wall of the stomach, as near to the pyloric end and the greater curvature as can easily be reached through an opening in the

mesocolon made to the left of the middle colic artery. The afferent loop is as short as possible. The efferent loop is most commonly turned to the right and passes downward and to the right in the general direction of the right iliac fossa. In exceptional cases the efferent loop is allowed to follow its natural inclination; it then passes downward and to the left in the general direction of the left iliac fossa. The pylorus is always excluded by the string method unless sufficient stenosis of its lumen already preëxists.

The operation of gastroenterostomy causes a distortion of the normal structure and contour of the stomach and of its anatomic relationships. This probably secondarily causes changes in the normal nervous mechanism controlling the normal gastric functions. Even when all the wounds are surgically healed in a manner most acceptable in the present state of our knowledge certain changes in the physiology are therefore inevitable because of this new anatomy. When superimposed upon the previously existing anteoperative deviations from the normal physiologic function the effects of the operation may be one of two: In many the immediate influence is of a beneficial nature and is amply demonstrated both by the subjective symptomatology and by the objective functional capacity of the stomach as determined by appropriate laboratory tests. In some the resultant immediate effect shows no improvement in the functions of the stomach from its preoperative status. In a very few an exaggeration of the latter status appears usually approximately equal to the old disturbances plus those due to the changed anatomy. The possible combinations probably furnish a very fertile field for the presence of postoperative symptoms.

This conception furnishes a ready explanation for the good results which usually follow a gastroenterostomy done for cicatricial pyloric stenosis; here an anatomic abnormality existing for a long period of time has caused accompanying changes in the normal physiologic mechanism, the progression of which holds an almost mathematic ratio with the degree and duration of the stenosis. After a certain time the disability reaches the point where the exhibited compensatory efforts of the stomach eagerly await a change in structure sufficient and competent to enable the organism to adjust itself satisfactorily to the new conditions. The gastroenterostomy accomplishes this in the most desirable way, and the postoperative compensation is therefore made with no or very little symptomatic disturbance.

The changes which follow gastroenterostomy have a wide latitude and can be considered from various viewpoints. The functional results were preliminarily studied without regard to the type of technic employed in the operation or to the secondary changes which had followed the essential ulcer pathology. Several tables

are appended in which this knowledge is summarized[1] (Fig. 2, 3 and 4).

Table II consists of cases in which at the time of the examination there were no subjective symptoms of any kind.

TABLE II.

MOTOR FUNCTION.

Case.	Roentgen-ray.			
	Pylorus.	Stoma.	Peristalsis.	Empty in.
4	Closed	Patient	Good	4 hours.
10	Patient	Patient	Fair	6 hours.
16	?	Patient	Good	6 hours.
19	?	Patient	Good	4 hours.
6	Patient	Patient	Good	?
22				

CHEMISM.

Case.	Fasting contents.			Ewald test-breakfast.			Riegel test-meal.		
	Residue in cc.	Free acid.	Total acid.	Residue in cc.	Free acid.	Total acid.	Residue in cc.	Free acid.	Total acid.
4	30	0	18	225	24	54	?		
10	30	4	10	70	50	86	0		
16	5	0	0	20	0	56	0		
19	10	0	0	60	0	14	?		
6	70	0	10	80	0	12	?		
22	25	10	22	75	16	46	?		

Table III includes cases in which an exhibition of symptoms indicated an incomplete readjustment to the new conditions either because of insufficient compensatory effort or because of the preoperative extraordinary degree of derangement. The studies seemed sufficient to make the assumption probable that no anatomic lesion was present. The degree of individual disturbance as indicated by the symptomatology showed wide variations.

[1] These tables should not be interpreted as indicating in any way the number or percentage relationships of the cases cured or not cured.

TABLE III.

MOTOR FUNCTION.

Case.	Roentgen-ray.			
	Pylorus.	Stoma.	Peristalsis.	Empty in.
2	Patent	Closed	Active	6 hours.
32	Patent	Patent	Active	6 hours.
5	Patent	Closed	Very active	?
12	Patent	Patent	Very active	¾ in 1 hour.
11	Patent	Not efficient	Very active	6 hours.
9	Patent	Not efficient	Fair	6+ hours.

CHEMISM.

Case.	Fasting contents.			Ewald Test-breakfast.			Riegel test-meal.		
	Residue in cc.	Free acid.	Total acid.	Residue in cc.	Free acid.	Total acid.	Residue in cc.	Free acid.	Total acid.
2	25	10	22	220	38	63			
32	25	12	30	60	16	65	40	14	30
5	90	46	48	300	44	64			
12	16	10	25	160	11	45			
11	65	21	41	125	36	68			
9	1	0	0	350	14	51	100	0	55

Table IV includes cases in which at secondary exploratory operations it was definitely proved that the symptomatology was directly due to anatomic lesions. In these cases also the degree of disturbance as indicated by the subjective symptomatology showed wide variations.

These tables demonstrate rather conclusively that the operation of gastroenterostomy, even when the postoperative course is seemingly ideal from every standpoint, is followed by certain changes in the physiologic mechanism of the stomach. The changes involve both the motor and chemical functions of the stomach, and it is not easy to distinguish the relative positions of either. It seems, however, from all that one knows that the motor function is most important for the proper working of the stomach; and it is more than probable that in many, if not in all, the chemical changes are secondary to the motor. The direction which the latter assume is toward a progressive retardation of the passage of the stomach contents onward in the alimentary canal.

With the appearance of postoperative symptoms of one kind or another a study of the individual functions indicates that the degree of physiologic derangement becomes progressively greater as the attempted readjustment is retarded or disturbed because of functional causes and reaches a maximum when the compensation is interfered with by the presence of mechanical obstacles to the proper motor functioning of the stomach (narrowing of the

stoma in the presence of a spontaneous or operatively produced pyloric obstruction).

TABLE IV.

Case.	Roentgen-ray.			
	Pylorus.	Stoma.	Peristalsis.	Empty in.
13	Patent	Not seen	Violent	6+ hours.
3				
14	Patent	Not seen	Violent	6+ hours.
18	Patent	Patent inefficient	Hyperperistalsis	?
24	Patent	Inefficient	Hyperperistalsis	6+ hours.
27	Patent	Patent	Active	6 hours.

CHEMISM.

Case.	Fasting contents.			Ewald test-breakfast.			Riegel test-meal.		
	Residue in cc.	Free acid.	Total acid.	Residue in cc.	Free acid.	Total acid.	Residue in cc.	Free acid.	Total acid.
13	44	8	21	190	30	64			
				450	30	50			
3	60	12	46	90	24	66	27	0	73
14	60	27	54	210	34	52			
18	50	27	41	200	39	53			
24	10	0	0	600	33	50	30	0	18
27	..	..	..	20	17	35	50	46	86

It seems to be true that in many of the cases in which these deviations from the normal take place the change becomes permanent. In a series of cases which were studied for periods up to four years after operation it could be demonstrated that while the chemical function remained practically in the same condition in which it was prior to operation the delay in emptying time, as demonstrated by test meals, persisted and grew larger as time went on. This is well shown in Table V. The roentgen-ray is not very reliable for determining this point, inasmuch as frequently the passage of a stomach tube is productive of stomach contents when no contrast meal is visible either fluoroscopically or on a photographic plate.[2]

TABLE V.

EWALD TEST-BREAKFAST.

	Residue in cc.	Free acid.	Total acid.
Before operation	74	47	72
1 to 4 months postoperative . .	127	27	61
4 to 12 months postoperative . .	148	27	54
1 to 4 years postoperative . .	190	32	60

[2] I am indebted to Dr. Held for this observation.

The subject under discussion might also be viewed with reference to the type of technic employed in the operation of gastroenterostomy. As indicated in the beginning of this communication this would enable a selection of that method of operating for routine purposes which would be followed most often by a minimum change from the normal standards; it was hoped that in that way the temporary or permanent disagreeable sequelæ, especially those in the period of readjustment after operation, might be obviated altogether or minimized as far as possible.

In most clinics the principal technics employed in gastroenterostomy include (*a*) posterior gastroenterostomy by suture or (*b*) by the Murphy button; (*c*) either of these in combination with a pyloric exclusion. The observations hereinafter summarized have to do with these three types of technic. In those cases in which ulcers were found and operations were done upon the stomach the patients were allowed to recuperate completely Then the functional capacity of the stomach was again determined in the manner previously alluded to.

In the suture gastroenterostomy cases in which no pyloric exclusion was practised the obtainable facts are gathered in Table VI and Fig. 2.

TABLE VI.

MOTOR FUNCTION.

Case.	Roentgen-ray.			
	Pylorus.	Stoma.	Peristalsis.	Empty in.
1	Open	Patent	Active	9 hours.
12	Open	Patent	?	¾ in 1 hour.
14	Open	Patent	Violent	6 hours.
25	Open	Patent	Very active	6¼ hours.
46	Open	Patent	Good	Over 6 hours.
64	Open	Patent	Good	Over 6¼ hours.

CHEMISM.

Case.	Fasting contents.			Ewald test-breakfast.			Riegel test-meal.		
	Residue in cc.	Free acid.	Total acid.	Residue in cc.	Free acid.	Total acid.	Residue in cc.	Free acid.	Total acid.
1	60	0	14	100	4	8			
12	20	16	25	160	11	45			
14	80	27	54	210	34	52			
25	25	18	31	70	32	94	25	36	62
46	35	42	60	40	30	50	0		
64	5	0	0	110	11	42	5	0	0

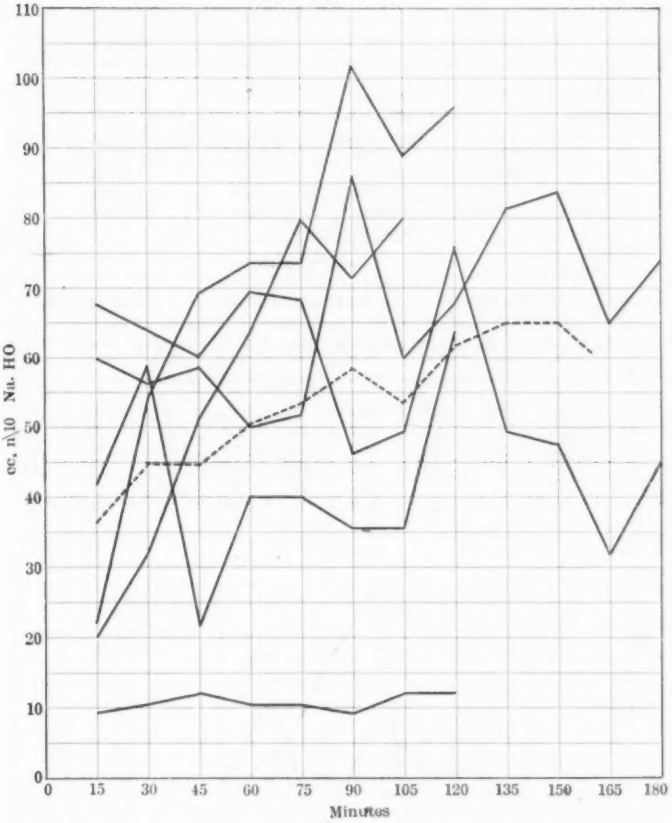

FIG. 2

In the second group of cases a pyloric exclusion by the string method was done in addition to the suture gastroenterostomy. The elicitable facts are summarized in Table VII and Fig. 3. A comparison of the observations in this group with those in the previous group enabled an evaluation of the effect of the string method of pyloric exclusion.

TABLE VII.

Case.	Roentgen-ray.			
	Pylorus.	Stoma.	Peristalsis.	Empty in.
4	Closed	Patent efficient	Good	4 hours.
2	Open	Not patent	Moderate	6 hours.
17	Closed	Patent	Fair	6+ hours.
39	Open +	Patent ++	Good	6½ hours.
53	Closed	Patent	Fair	6½ hours.
66	Closed	Patent	Fair	6 hours.

Chemism.

Case.	Fasting contents.			Ewald test-breakfast.			Riegel test-meal.		
	Residue in cc.	Free acid.	Total acid.	Residue in cc.	Free acid.	Total acid.	Residue in cc.	Free acid.	Total acid.
4	27	13	30	350	20	45	60	0	27
2	26	10	22	200	38	63	58	0	16
17	75	22	40	150	50	71	70	58	83
39	30	60	80	110	68	96	40	14	50
53	0	..	..	265	30	48	0		
66	0	..	..	100	15	60	50	38	47

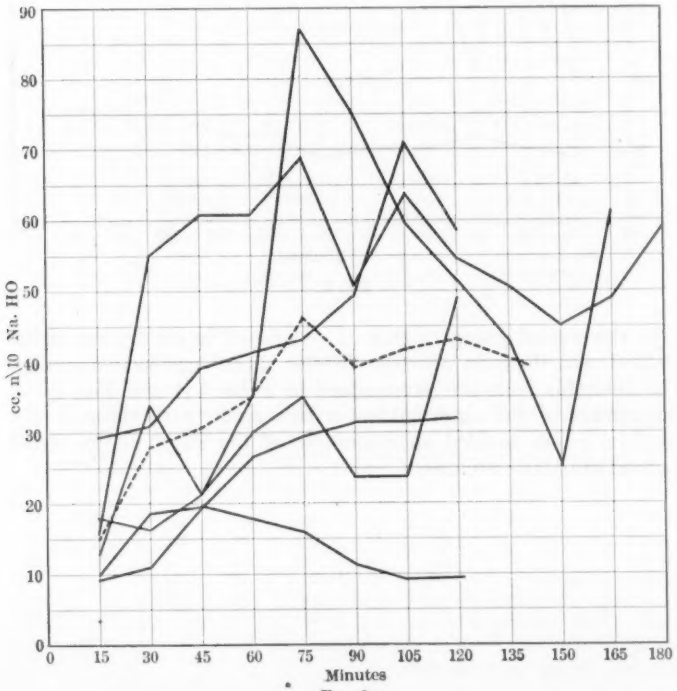

Fig. 3

In the third group the gastroenterostomy had been made with the aid of a Murphy button and a pyloric exclusion had been made with the technic described in the previous paragraph. The facts are grouped in Table VIII and Fig. 4. A comparison between the second and third groups enabled a judgment as to whether the suture or button operation was superior.

TABLE VIII.

MOTOR FUNCTION.

Case.	Roentgen-ray.			
	Pylorus.	Stoma.	Peristalsis.	Empty in.
10	Open ++	Patent +	Good	6 hours.
16	?	Patent	Good	6 hours.
22	Closed	Patent	Active	6 hours.
48	Open	Not seen	Fair	
55	Open	Not seen	Fair	6 hours.
50	Closed	Patent	Active	6 hours.

CHEMISM.

Case.	Fasting contents.			Ewald test-breakfast.			Riegel test-meal.		
	Residue in cc.	Free acid.	Total acid.	Residue in cc.	Free acid.	Total acid.	Residue in cc.	Free acid.	Total acid.
10	30	4	10	70	50	86	0		
16	5	(mucus)	..	100	0	50	0		
22	16	0	?	70	4	50	15	34	52
48	0	..	..	180	66	88	35	34	52
55	15	8	24	150	38	76	50	68	90
50	0	..	..	30	28	52	90	56	74

The average findings in the three groups studied are compared in Table IX. In a general way these observations correspond with those noted in the earlier tables; there are larger residues after the various test meals, and the general run of acid concentrations does not show much deviation. In the individual groups it is to be noted in most of the cases that the suture operations yield a larger residue after the test meals when an exclusion has been simultaneously practised. In contradistinction to these two groups of suture operations the button operations seem to yield residues which more nearly approach the normal. The smallest fasting stomach contents is obtained after the button operation. The average functional result after a suture operation without an exclusion seems to equal that of a button operation with an exclusion.

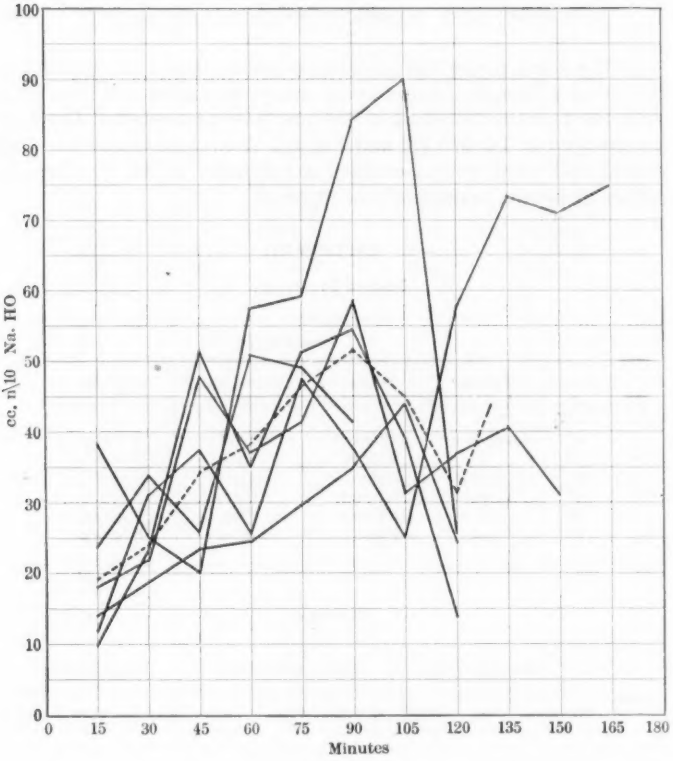

FIG. 4

TABLE IX.

MOTOR FUNCTION.

Table.	Roentgen-ray.				Emptying time by fractional test meal.
	Tone.	Stoma.	Peristalsis.	Empty in.	
1	Good	..	Active	5¼ hours.	2 hours, 5 minutes.
6	Good	..	Very active	6⅔ hours	2 hours, 9 minutes.
7	Fair	..	Moderate to fair	5⅔ hours	2 hours, 22 minutes.
8	Good	..	Active	6 hours	2 hours, 5 minutes.

CHEMISM.

Table.	Fasting contents.			Ewald test-breakfast.			Riegel test-meal.		
	Residue in cc.	Free acid.	Total acid.	Residue in cc.	Free acid.	Total acid.	Residue in cc.	Free acid.	Total acid.
1	0	..	..	50	35	59	0		
6	37+	17+	30+	115	20	48+	10	18	31
7	26+	26+	53	177+	36+	63+	46	22	44+
8	11	6	17	100	31	65+	31+	48	69+

After a suture operation the roentgenographic evidence indicates that peristalsis becomes excessive and in some cases violent. Even with this increase in muscular effort, however, the total effect as regards the emptying time of the stomach does not show any appreciable advance over the preoperative status; in some, indeed, it is lengthened. When an exclusion has been practised the muscular effort gives evidence of some inhibition. In either case it seems that the total efficiency of the stomach as a machine whose function is to empty itself in a given time, is disturbed. With the button operations the roentgenographic evidence indicates that the contractions of the stomach wall most nearly approaches the preoperative normal standards, and the total efficiency seems least disturbed.

When considering these observations from the point of view of the kind of operation employed it becomes necessary to give much attention to the size of the stoma, to the ease with which stomach contents can engage in its lumen and pass onward in the alimentary canal, to the presence or absence of an open pylorus, and to the presence or absence of deformity of gastric contour. In the cases discussed in this communication no case with any deformity of contour has been included. The cases with spontaneously produced and preëxisting pyloric stenosis were also discussed previously. In the acute pyloric occlusion produced in the exclusion operation the evidence indicates that some disturbances may be expected owing to the fact that the stomach is not adequately prepared for this anatomic change; time must be given for complete compensatory readjustment.

The physical characteristics of the stoma are matters of importance in its proper functioning. It is important that no spur be created and that no superabundance of gastric mucosal folding be present and capable of falling across the mouth of the stoma with the formation of a valvular mechanism; in either case the passage of stomach contents would be impeded. The size of the stoma is most important. When studying the subject with the roentgen ray it is to be noted that in some of the cases the major portion of the contrast meal pours through the stoma in a large stream into the small intestine at a very rapid rate; the stomach is practically empty in a comparatively few minutes. In others of the cases a small amount remains in the stomach after the initial rapid outpouring of the contrast meal, and for some unaccountable reason takes a comparatively long time to be evacuated completely. Clinically the cases with such rapid outpouring and emptying frequently have distressing symptoms. In these cases the stoma is manifestly too large. Many experiences have indicated that a stoma which is too large is just as bad—if it be not worse—as one which is too small; a happy medium is desirable.

In fashioning the stoma with the button the finally resulting

opening is just large enough to admit an average-sized forefinger. This corresponds rather accurately with the size of the normal pylorus. The opening made with the suture method is always much larger than this; in most clinics the stoma is made large enough to admit easily two average-sized fingers. This means a very large difference when one takes into account the number of muscle and nerve bundles divided; with the button a small incision is made and the latter is then bluntly dilated sufficient to admit the button; with the suture much more than two fingers' breadth must be cut in order to allow for subsequent contraction. I am inclined to think that for this reason the functioning of a button stoma shows a nearer approach to the normal standard; its action more nearly approaches that of the pylorus.

Summary. Evidence is presented which seems to show that the functional result of a gastroenterostomy made with the aid of a Murphy button is superior to that of a gastroenterostomy made by the suture method.

THE MALE SEXUAL GLAND IN THE PREVENTION OF CREATINURIA.*

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The perplexing problems of the origin and intermediary metabolism of creatin and the factors influencing its excretion have not been definitely solved, in spite of the mass of investigative work. Creatin is found normally in animal tissue, specially muscle, in the urine of children, and occasionally in the urine of normal women. Only under certain pathologic conditions, such as fasting, cachexia, febrile disease, hyperthyroidism, diabetes mellitus, myopathies and so forth does the adult male excrete creatin. "Since creatinuria disappears at puberty, and does not occur in normal man, a hitherto neglected factor for its excretion obtrudes itself, namely, the influence of the male sexual gland.[1]"

In order to determine the effect of castration on the creatin excretion of the rabbit, experiments initiated August 1, 1920, were carried out at the Sprague Memorial Hospital of Chicago, in conjunction with Dr. George H. Jackson, Jr. In some instances there was a pronounced increase of creatin excretion on the second day following castration, and possibly a slight persisting increase lasting forty-five days. These experiments were controlled by

* This work was undertaken at the suggestion of Dr. S. Amberg, to whom I wish to acknowledge helpful suggestions given during the course of the study.

similar experiments on rabbits in which the vas deferens was tied off. The results were only suggestive at best. Such experiments should be repeated on animals that normally do not excrete creatin, as the onset of creatinuria gives results more definite than a condition in which the normal amount of creatin is increased. Such conditions exist in man.

Beginning in February, 1921, we have had the opportunity in the Mayo Clinic of studying the creatin excretion of two eunuchs, three men with a congenital testicular defect and one man with a defect acquired at the age of twenty-seven years. We had completed the rabbit experiments, the observations on one eunuch, and on one person with a congenital testicular defect, when the very interesting paper of Read appeared. Having the same idea in mind, Read had studied the creatin excretion of the Chinese eunuch; he found that creatin was constantly present in the urine of eunuchs who had been castrated before the development of the secondary sex characteristics. His results are tabulated:

TABLE 1.

Eunuch.	Age.	Age at operation.	Excretion of		
			Nitrogen, gm.	Creatinin, per cent.	Creatin, per cent.
2	18	12	7.12	Trace	0.149
3	18	9	4.09	0.204	0.424
4	30	19	....	0.039	0.060
5	27	?	....	0.006	0.017
6	40	29	....	0.004	

The heading per cent, under which the creatinin and creatin values are given, we assume to mean total output in milligrams. The creatinin and creatin values are very remarkable. Read states that the absence of creatinuria in eunuch 6 is owing to the fact that castration was performed at the age of twenty-nine years, after the development of the secondary male characteristics. As the sexual maturity of the Chinese race is late, the infantile influence on creatin metabolism was still present in eunuch 4 at the time of castration performed as late as the nineteenth year. Therefore, he continued to excrete creatin for the same reason as eunuch 3, castrated at nine years.

In each of our six patients one specimen of urine was analyzed for creatin immediately after voiding; the results correspond with the subsequent determinations. The twenty-four-hour specimens of urine were collected in a bottle containing toluol and surrounded by ice. Folin's method was used for the determination of the creatinin and creatin and Folin's micro Kjeldahl method for the determination of the nitrogen. The patients were on a general diet, on which normal man does not excrete creatin.

Report of Cases

Case 1.—(A344023) H. E. B., aged thirty-one years, was unmarried. He had been in good health, and normal sexually, until February, 1918, when, following a therapeutic accident, it was necessary to remove completely the testicles, scrotum, and penis. His libido remained. The patient was muscular, and unusually fat around the face and neck; this had increased since castration He was a blond, had very little hair on the body, but the normal amount on the head and face and in the armpits. He was treated for chronic granuloma in the region of the operation. The analysis of his urine is shown in Table 2.

TABLE 2.

March.	Nitrogen, gm.	Creatinin, mg.	Creatin, mg.
5	8.59	1169	124.3
6	13.8	1535	115.0
7	9.53	1352	59.0
8	9.68	1518	52.8
9	11.99	1412	53.8
11	12.09	1190	137.3

Case 2.—(A354881) W. D. E., aged forty-two years, had been married eleven years and had not had children. Sexual incompetence and a minimum of libido had always existed. His build was of the feminine type, with broad pelvis, hypotonicity of the musculature, and an accumulation of fat in the breasts and buttocks. There was no hair on the body, a normal amount in the armpits, and a scant growth on the head and face. He said that there had been scarcely any change in his appearance during the past twenty years. The testicles were pea-sized; the penis was small. The basal metabolic rate was −15 per cent. The analysis of the urine is shown in Table 3.

TABLE 3.

	April.	Nitrogen, gm.	Creatinin, mg.	Creatin. mg.
	23	6.13	1221	117.6
	24	12.14	1446	98.6
	26	23.18	1699	339.9
	27	11.63	1428	140.0
Thyroid extract, 5 grains	28	14.28	1500	192.0
Thyroid extract, 5 grains	29	18.79	1433	75.4
	30	7.59	1499	322.0
	May			
	2	11.55	1584	561.0
	3	8.31	1397	479.4

Case 3.—(A330908) C. H. H., aged thirty-nine years, had been married five years and had not had children. At the age of thirteen

the testicles had been swollen and painful for a short time. At the age of twenty-seven a syphilitic infection occurred. For the last eight years sexual incompetence had gradually increased, becoming marked during the last two years. The beard and the hair under the arms had disappeared at the onset of sexual incompetence. The patient was masculine in build. The testicles and penis were small. The basal metabolic rate was −31 per cent. Polydipsia and polyuria had existed for several years and the response to injections of pituitrin justified a diagnosis of diabetes insipidus. The findings of the cerebrospinal fluid were those of cerebrospinal syphilis. The analysis of the urine is shown in Table 4.

TABLE 4.

March.	Nitrogen, gm.	Creatinin, mg.	Creatin, mg.
5	7.67	1650	132.0
6	5.38	1347	73.6
7	6.85	1349	28.5
8	9.68	1518	52.8
9	3.23	555	49.5

CASE 4.—(A375931) R. N., aged thirty years, unmarried, had always been in good general health. Potentia and libido had never been present. His general build was feminine, with broad pelvis, narrow shoulders and a marked accumulation of fat in the breasts. He had no hair in armpits or on face, and it was sparse on the pubes. The testicles were pea-sized, and the penis about 2.5 cm. in length. The prostate was not palpable. His voice was high-pitched; he appeared to be about seventeen years of age. The analysis of the patient's urine is shown in Table 5.

TABLE 5.

July.	Nitrogen, gm.	Creatinin, mg.	Creatin, mg.
19	11.9	1422	154.0
20	7.4	1230	98.0
21	9.6	1430	91.0

CASE 5.—(A367481) J. K., aged fifty-one years, had always been in good general health. Following a gonorrheal infection twenty-three years before, he had developed painful, chronic epididymitis, for which castration was performed four years before examination at the Clinic. He had been sexually normal, but after the operation libido and potentia were lost. The examination was negative except for moderate adiposity and evidences of a chronic prostatitis. The patient did not remain under observation long enough so that a twenty-four-hour specimen of urine could be obtained. The results of the analysis of two freshly voided specimens are shown in Table 6.

TABLE 6.

	Nitrogen, gm. for each 100 cc.	Creatinin, mg. for each 100 cc.	Creatin, mg. for each 100 cc.
Day specimen	2.48	322	15.9
Night specimen	3.89	247	6.3

CASE 6. (A375931) W. R. M., aged thirty-seven years, was unmarried, and had always been in good health. Libido and potentia had always been absent. He was very tall and thin, with narrow shoulders. He was well developed muscularly. He appeared youthful, and his voice was high-pitched. He had only a few hairs on the pubes and in the axillæ. The testicles were pea-sized and the penis very small. The basal metabolic rate was −10 per cent. The patient represented a typical picture of a eunuchoid giant. The analysis of the urine is shown in Table 7.

TABLE 7.

October.	Nitrogen, gm.	Creatinin, mg.	Creatin, mg.
29	10.78	1800	98
30	12.46	1896	147

The men (Cases 1 and 5) who were castrated at the ages of twenty-nine and forty-seven years respectively, excreted creatin. This is in contradistinction to the observations of Read, who asserts that creatinuria occurs only in eunuchs in whom castration is performed before sexual maturity. Analysis of the urine of three men with congenital testicular defects, and of one with a deficiency acquired at the aged of thirty-one, showed the presence of creatin regularly.

We had hoped to report a parallel series of cases with loss of libido and potentia, on a functional basis, and not dependent on an organic defect. Unfortunately, we had the opportunity to study only one such person. He had been healthy and normal sexually until July, 1921, when he discovered on one testicle a small swelling (spermatocele). After that, libido and potentia were wholly lost. The physical examination was negative. Creatin was not found in this patient's urine.

Discussion.—The creatin output varied markedly in the same patient from day to day and bore no relation to the total nitrogen and fairly constant creatinin values.

It is of interest to note that during the observation of Case 2, particularly high creatin values were obtained following the administration of thyroid extract for two days.

It is to be noted that all the cases were free from any condition with which creatinuria in man had been described, such as hyper-

thyroidism, diabetes mellitus, cachexia, disease of the liver, febrile disease, or primary and secondary myopathies.

Besides the sexual incompetence on an organic basis in Case 3, a diagnosis of diabetes insipidus was made. In view of the fact that creatinuria occurs in association with diseases of three other endocrine glands (thyroid, pancreas, and male gonad), it seems quite possible that the disturbance of the pituitary gland may have exerted additional influence in the production of the creatinuria.

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A CLINICAL AND PATHOLOGICAL STUDY OF NEURITIS IN THE TROPICS, WITH SPECIAL REFERENCE TO BERIBERI.

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Introductory Note. This clinical and pathological study represents our crystallized opinions upon the principal problems connected with the subject, after prolonged residence in the tropics in teaching, research and practice.

No attempt is made to review the literature or to cover the practical field completely.

It is our aim to elucidate "Neuritis in the Tropics" rather than "Tropical Neuritis," and to clarify as much as may be this exceedingly difficult subject.

Of the problems of tropical pathology, that of neuritis is one of the most interesting, baffling and important. It is still very far from being solved.

The literature on the subject is enormous and much of it is of little value. Perhaps in no other field do we see so much uncontrolled, incomplete or unreliable work used as a basis for so many

varied and often unwarranted conclusions. On the other hand, splendid, careful research has been done both in the laboratory and clinical fields, and contributions are being made which tend to simplify the problem. In fact, in some of its most important phases solution is already in sight.

At the very beginning of our problem we encountered difficulties in classification. While we know that etiologically there is more than one disease in the group of the neurites, neither by a study of the clinical picture nor the pathology have we information which clearly distinguishes between some varieties of known etiologic difference, much less between those of unknown causes. Sometimes it even is exceedingly difficult to state that a given picture in reality is neuritis.

Nevertheless, the only sound classifications are those based upon etiologic grounds, and to do this we must at times accept hypotheses tentatively as facts or classify arbitrarily. The problem is more complex in the tropics than it is in temperate climates because of the great prevalence of the endemic neuritis, generally called beriberi.

We shall be guided in our discussion by the following outline:

Etiological Classification of Multiple Neuritis

A. *Intrinsic Factors:*
   Heredity (anatomic, physiologic and social status).

B. *Physical Agents:*
   Traumatism and pressure.
   Meteorologic and climatic conditions (altitude, atmospheric pressure, heat, cold, moisture, winds).
   Occupation, electricity.
   Environment in general.

C. *Chemical Poisons:*
   Inorganic (arsenic, lead, etc.).
   Organic (alcohol, etc.).

D. *Intoxications:*
   Exogenous—food and other substances already poisonous when taken, toxins formed in various ways in the alimentary canal.
   Endogenous (excluding toxins of known biologic agents):
      1. Toxins formed within the body and due to derangement of metabolism, in nephritis, anemia, etc.
      2. Internal secretion disturbances.

E. *Biologic Agents* (including their toxins):
   Animal—syphilis, malaria, hookworm, schistosoma, trypanosoma, etc.
   Vegetable—tuberculosis, typhoid, diphtheria, undulant fever, leprosy, etc.

F. *Metabolism Disturbances Due to Faulty Food Balance:*
Neuritis in pregnant and parturient women.
Neuritis in nursing infants.
Endemic tropical neuritis, beriberi.

Most of the etiologic factors shown in the table, and which are concerned in the production of neuritis in other countries, must be reckoned with in a study of the disease as it exists in the tropics. The most careful direct search for the etiology in each case of neuritis and a diagnosis only after the most exhaustive study and elimination is specially urgent in the tropics, and, if done, will give two very desirable results: It will change the present custom of diagnosing practically all cases of neuritis as beriberi, and it will result in simplifying the beriberi problem by harmonizing the results of investigation.

Intrinsic Factors. Conditions inherent in the patient, including hereditary influences and possible intrauterine diseases, must be important predisposing factors in at least certain classes of neuritis.

The report of the government committees for the investigation of infant mortality in the Philippine Islands records an average intrauterine death-rate of over 30 per cent. The causes of these deaths are in part at least unknown, and a predisposing influence to disease of the nervous system among those who do not die is generally recognized.

The anatomic, physiologic and social status as it has been evolved out of a poor heredity, disease and all but universal malnutrition might well be supposed to leave the nervous system particularly susceptible to neuritis as we know it leaves other parts of the body for other diseases. Indeed, histologists are frequently surprised in their study of supposedly normal histologic tropical material to find the nerves abnormal and even at times showing the picture of neuritis.

Neuritis Caused by Physical Agents. It is probable that physical agents are more important factors in the production of neuritis in the tropics than elsewhere. This may be due in part to special environment, and there are facts which indicate that neuritis may be produced in an Oriental by conditions which would rarely lead to such a result in temperate climates.

As an example, neuritis of the lower extremities is quite frequent during the latter months of pregnancy. In many instances the complication may be beriberi. Apart from this phase, which will be discussed under beriberi, there is a considerable number of these varieties that have little resemblance to beriberi. There are no cardiac symptoms or other evidences pointing to a serious condition. They appear to be due to pelvic pressure and to the water-logged edema of the dependent parts. This condition, noted but rarely in temperate climates, is quite prevalent in the tropics.

Neuritis from pressure by tumors, aneurysms and tight bands worn by certain tropical people is noted occasionally, and it sometimes follows the extensive traumatic wounds so frequently encountered in the land of the bolo and the kris.

Posture has been thought to be a factor in the preponderating prevalence of neuritis of the lower extremities over that of other parts of the body. Most Orientals rest in the squatting position instead of upon a chair, and they may remain comfortable in such position for hours at a time. Acosta-Sison considers this fact responsible for the very great prevalence of malpositions of the uterus among Filipino women.

Sudden changes from the lowlands to the cool high altitude hill stations is associated with the development of neuritis too often to be explained by coincidence.

Other meteorologic and climatic conditions influence the progress of neuritis, and the sudden changes so often seen in the tropics from hot and dry to cool and humid, although slight as compared with similar changes in colder countries, nevertheless produce most profound effects upon people and may not be disregarded in considering the onset of neuritis.

What in a general sense may be termed tropical environment exerts a powerful and constantly acting adverse influence upon the nervous system of all persons. Just what particular factor or factors in the environment are most to blame is not fully understood, but it is probable that it is the composite picture made up of heat, moisture, sudden change, mode of living, worries and fretting, and the squalor, ignorance, poverty, mixed languages and general unestheticness of the whole thing—all acting together—that racks the nervous system of the foreigner and influences the propagation of the weak, emotional, unstable, hysteric type so general among Orientals. It perhaps would be going too far to say that these conditions are the actual causes of neuritis, but that they so successfully prepare the way that otherwise innocuous agents may bring it about seems likely.

Neuritis Caused by Inorganic Chemical Poisons. The only known variety of particular importance in the tropics is arsenic neuritis, and the careful observer finds this quite frequently. At one time arsenic was considered to be a cause of beriberi. Arsenic is used extensively by many of the dark-skinned races as a medicine to be taken internally and in lotions and powders for the skin. Its skin-bleaching properties are widely known, and frequently enormous amounts are used to lighten the color of the skin, which is the vain ambition of every native woman.

Lead paints and lead work in general is not extensively applied in the Orient and lead neuritis rarely is seen.

Neuritis Caused by Organic Chemicals. Alcoholic neuritis is the most prevalent type in this group, just as it is in other countries.

It is generally stated that tropical people are not important consumers of alcohol. This oft-repeated statement is open to serious doubt. Imported and taxable alcohols for beverages average about three-eighths less per capita in the Philippine Islands, for example, than in the United States. However, in making comparisons it must be remembered that the average size of Orientals is only a little over two-thirds that of Americans, that their nervous systems are more sensitive and that the effects of alcohol upon any person is greater than it is in a cold country. Furthermore, the most prevalent alcohols consumed by the great mass of Orientals are not taxable and not therefore included in statistics. There are a considerable number of home-made preparations of alcohol, from the palm, sugar cane, etc., that are just as effective, probably more so, in producing neuritis as the imported varieties.

In any event, alcoholic neuritis is quite frequently seen in our large clinics among all classes, and in most instances a tentative diagnosis of beriberi is made. A supposedly typical case of beriberi was used in a clinic for senior medical students. The instructor felt humiliated when positive evidence was secured that the patient was a gin-drinker and had averaged nearly a quart of gin a day for several years.

Neuritis due to the other recognized organic chemicals is not frequent enough to be of importance. However, there is a great practically unexplained field among the unknown local herbs used as medicine. Practically all Orientals are extensive users of "herbs" as medicine. Most trees, flowers, weeds, as well as many fish, insects and minerals, are included in this group of cure-alls. Some of these substances are known to contain active poisons, and many others no doubt belong to the same group.

Neuritis Due to Intoxication. Toxins introduced in food or formed in and absorbed from the alimentary canal are a vastly more important subject in the tropics than elsewhere. That neuritis may be caused by such direct intoxication seems likely. The activities of the great variety of capsulated aneurotic bacteria constantly forming part of the tropical intestinal flora offers a promising field for investigation.

"Ptomain" poisonings are exceedingly common, and the enormous prevalence in the tropics of intestinal derangements due to infections and to the questionable quality of much of the food eaten by the poor makes it likely that this subject is more important in the etiology of neuritis than we now realize.

Endogenous toxins formed as products of disease or from deranged metabolism caused by disease assumes special importance in the tropical problem of neuritis. In addition to such diseases as diabetes, rheumatism and nephritis we have an unusual number of anemias, cachexias, fevers and other pathologic conditions of unknown cause which are not infrequently forerunners of neuritis.

The recognized excess of lymphoid tissues, forerunners of the hyperactivity of ductless glands and consequent instability of internal secretions, constitutes an enticing field for tropical investigation, and is looked upon with suspicion as an influence in the production of tropical neuritis.

Neuritis Caused by Biologic Agents. Animal parasites, such as those causing syphilis, yaws, malaria, trypanosomiasis and schistosomiasis in particular, acting either directly or through their toxins, are the exciting causes of a certain percentage of neuritis. Other animal parasites, including the various intestinal worms, exert a pronounced effect upon the nervous system, particularly in children, and it is probable that they at times may be considered the exciting cause of neuritis.

Bacteria and other vegetable parasites which cause tuberculosis, leprosy, pneumonia, typhoid, influenza, whooping-cough, undulant fever, and gonorrhea in particular, are recognized as the exciting causes of neuritis. In this role they may act directly, as in the case of the leprosy bacillus, or indirectly through their toxins, as shown for example in the diphtheria toxin.

The unknown causative agents of certain other diseases, as smallpox and dengue-like fevers, also must be considered among the causes of neuritis.

As in the well-known cause of typhoid neuritis the bacteria must not bear the entire blame for the neuritis, which in reality often is due to the action of the bacteria in the presence of a nutritional deficiency caused by insufficient or improper food.

Incidence. The various forms of neuritis discussed up to this point have a much higher incidence in the tropics than is generally recognized. Except in clinics and in hospitals there seems to be a remarkable tendency to diagnose all of them as beriberi without further investigation. During one period of about six months a careful study of patients admitted to our service with a previous diagnosis of beriberi showed over 50 per cent of them to belong in other groups.

The clinical varieties of acute, chronic and residual conditions seen in neuritis elsewhere are found among those in the tropics. The clinical picture otherwise, as well as the pathology, prognosis and treatment, do not differ sufficiently from similar conditions in temperate climates to warrant special attention here. Diagnosis is more difficult, much more difficult, and will be considered in the discussion on beriberi.

After we have studied a series of cases of neuritis in a tropical community by all the means at our command, and have classified them as far as possible into groups of known causes, there still remains a very large proportion unaccounted for, and these we will consider under the most used name of beriberi.

Beriberi.

Synonyms—Definitions—General Remarks.
Predisposing Causes:
Inherited and prenatal factors (breeding, constitution, temperament, etc.).
Physical factors (climate, meteorology, geography, etc.).
Social factors (age, race, sex, poverty, etc.).
Public health factors (sanitation, overcrowding, prisons, etc.).
Personal hygiene and personal health factors.
Incidence, predisposition and immunity.
Exciting Causes:
Brief review of the various theories.
Discussion of the various theories.
As a group disease.
Summary of present knowledge, conclusions.
Pathological Anatomy.
Symptomatology (introductory remarks):
Clinical types: Acute, chronic, rudimentary, residual conditions.
Complications (diagnosis, prognosis).
Prevention (public health measures, personal measures).
Treatment.

Synonyms. Kakke, asjike, loempe, endemic multiple neuritis, panneuritis endemica and many, many others.

Definition. A chronic or less frequently acute disease or group of diseases caused in whole or in part by faulty food supply, assimilation or metabolism. It is characterized pathologically by a multiple neuritis selective in type for the pneumogastric, phrenic, anterior tibial and peroneal nerves, but extending to other nerves as well; expressed clinically by edema, pain, paresthesias and absence of reflexes, particularly in the lower extremities, palpitation and dilatation of the heart, epigastric distress and absence of fever. It is endemic in most Tropical and Oriental countries and finds its highest incidence among the ignorant and exceedingly poor.

General Remarks. Beriberi is one of three or four diseases which, taken together, always have stood as an insurmountable barrier against progress, civic, economic and social, throughout the great Tropical and Oriental world. It is a large factor in the physical imperfection, mental primitiveness, social degradation, economic squalor and sanitary backwardness of the population of these countries. The history of the disease is well told in Vedder's excellent monograph on the subject. It has been known and something of its ravages recognized in China, Japan and probably elsewhere almost since the beginning of the Christian era. Practically no Oriental, Tropical or far-eastern country ever is free from

it. It occurs sporadically, endemically and pandemically. Without being contagious or infectious, it rises and falls and passes in great waves over vast territories of hundreds of millions of inhabitants. Its association with ignorance, squalor and poverty is so close and intimate that its statistical diagram might be taken as an index of the intelligence and progress of a community.

Predisposition and Immunity. Certain races appear to have a natural immunity against the disease, and certain of the Tropical races seem to be especially susceptible to it. Newcomers into a beriberi zone, whether of foreign or native birth, seem to be less susceptible in certain instances, while in others similar change appears to increase the risk to the immigrants. It is probable, however, that all of these observations may be satisfactorily explained by other forces than predisposition and immunity. One or a number of attacks of the disease does not produce immunity, and it is likely that no such quality exists.

Etiology (Predisposing Causes), *Prenatal Influence.* We have not sufficient evidence to justify a positive statement that there is anything in inheritance or prenatal disease which predisposes to beriberi. However, the frequency of the condition in infants and other facts point to the existence of some such influence.

The frightful infant mortality in all tropical countries, due in large part to the poverty and squalor of the people and the consequent physical unfitness of mothers, and particularly the sacrifice of intrauterine life from similar causes, which constitutes over 30 per cent of the fetal death-rate in the Philippine Islands, strongly suggests that prenatal conditions are in part responsible for the high incidence of beriberi under certain conditions and among certain people.

Physical Conditions. Beriberi finds its highest incidence under certain physiographic conditions, climate and rainfall, and is largely confined within certain geographic limits.

Environment favorable to the spread of beriberi is that generally described as the East, the Orient or the Tropics. This does not necessarily mean climate, heat, geography, rainfall, customs of the people, activities, energies or any other one thing, but a conglomeration of these and many others which molds all classes who dwell in it to a something in common or destroys them. This environment is the home of beriberi, as it is of so many other diseases and abnormalities.

The disease is common in the entire Malay Archipelago, India, Burmah, Ceylon, China, Japan, the Philippine Islands, Dutch Indies, Korea, Siam, New Zealand, Australia, Africa, South Sea Islands, South America and on ships in various seas. In some countries it is limited to certain areas, and outbreaks are recorded in many parts of the world.

Seasonally, beriberi appears to be a wet-weather disease. In

endemic areas it is found at all times of the year, but in most places from which we have reliable statistics it reaches its highest incidence during and just after the rainy season. There are exceptions to this rule, and in some locations variation in rainfall is not sufficient to warrant emphasis on the wet season. In the Philippine Islands the incidence curve is highest toward the end and shortly after the rainy season, but the difference is not striking, and some of the past epidemics have continued through more than one season.

Other physical conditions which seem to be associated with the prevalence of beriberi are shown in its selection of lowland and river valleys, being less prevalent in high altitudes and in interior cities.

Social Conditions. The disease may occur at any age and in both sexes, but it is much more prevalent among young adult males and during early infancy. It is rare among very old people, and, except the infantile variety, it is less frequent during childhood. While all races are susceptible the dark-skinned tropical people are the greatest sufferers, and in given localities certain nationals seem more susceptible than others. Thus Bradden notes that while the native Malayan suffers but little, Chinese immigrants in the Straits and Malay Archipelago show a high incidence and a high mortality rate. In the Philippine Islands the native Filipinos are the greatest sufferers, the Japanese come next, and the disease is comparatively rare among the Chinese. Members of the white race rarely contract the disease.

Occupation. The disease is rare in all countries among merchants, artisans, professional men and in general among members of the social upper strata. It reaches its highest incidence among teamsters, farmers, rice-workers and others of the unskilled-labor classes.

Poverty. Beriberi is *par excellence* a disease of the poor, ignorant and superstitious, and is comparatively rare among any other class in any country. The poverty factor of greatest importance is that of quality and quantity of food supply. Poor people buy and eat almost without question what their local community markets supply, and this varies in volume, nutritional value and balance, always being deficient in proteins and fats.

Public Health Conditions. Beriberi subjects, regardless of race or residence, belong largely to the class who constantly infringe every sanitary requirement. They are mostly residents of the slums of the great Oriental and tropical cities, which means the worst that can be imagined for human beings. The worst areas are most frequently located on low shore land, with dirty, crooked, unpaved alleys for roadways, without any or with inadequate water supply or appropriate means for handling sewage and garbage. House construction is of the adobe stone without proper foundation or elevation, with dark, damp, poorly ventilated rooms, shared by human beings and animals alike; or, in certain other

localities, house construction is of bamboo or grass. Water is carried from a distance and stands in dirty barrels or earthenware pots; the local markets are dirty and the insect-covered and dust-covered food handled and examined freely by the different purchasers.

Overcrowding. Overcrowding is the rule in the slums of all Oriental cities. House-sleeping capacity is measured frequently by as many persons as may have pallet room on the floor, both sexes, children, sick and well, sleeping together indiscriminately in closed rooms. Only too frequently public buildings, such as barracks, prisons, theaters, amusement halls, etc., are not much of an improvement on the home conditions of these people, and overcrowding in such places is the rule in many communities. Millions of people live under conditions where there is no such thing as cleanliness, as the Occidental understands the word, and where there is no such thing as health, as he understands the term. These conditions, with variations to meet local custom, give beriberi its highest incidence and are responsible for the former hypothesis that it was a *place disease*. Existence under such circumstances may well be a predisposing factor to any disease, including beriberi.

Personal Health and Hygiene. Other diseases are not known to predispose to beriberi. Aside from its prevalence among pregnant and parturient women, it attacks persons otherwise apparently in normal health as frequently as it does weaklings. However, various diseases and depressing influences, such as the acute infections, mental exertion, emotion and excesses of all kinds, are considered by Scheube and others as predisposing factors.

Exciting Causes. As in many another disease for which a definite cause has not been determined, the theories concerning the etiology of beriberi are almost as numerous as its investigators. Each of these theories has been valuable insofar as it has led to accurate investigation of particular phases of the disease and the conditions surrounding its onset and occurrence. In this way, the list of possible causes has been narrowed down to relatively few. Thus far study of changes produced in the patient by the disease has furnished little that throws light on the true immediate causative factor, although predisposing influences have thus been detected. Rather a study of the external conditions surrounding the patient, and especially a study of the epidemiology, including diets, has been fruitful in furnishing satisfactory working hypotheses, at least concerning the cause of the disease, its prevention and its treatment.

While it probably is true that the exact determining cause of beriberi has not yet been absolutely proved, yet we are of the opinion that our present knowledge is sufficient to render some of the theories as to its etiology of more than historic interest. Ven-

turing upon this assumption, we will be satisfied with a simple classification of the various theories and will make particular mention of only those which have been of importance in leading us to our present state of knowledge and those which are associated with the names of investigators whose names in themselves entitle their theories to our respect.

THEORIES CONCERNING ETIOLOGY OF BERIBERI.

A. *Intoxication:*
1. Inorganic chemical.
   (*a*) Arsenic: Ross.
   (*b*) Carbon dioxide: Ashmead.
   (*c*) Oxalate: Trentlein, Maurer.
2. Organic.
   (1) Vegetable.
      (*a*) Spoiled rice: Braddon, Fletcher, Breandat, Gelpke.
      (*b*) Ptomains.
      (*c*) Other poisons.
   (2) Animal.
      (*a*) Fish: Gelpke, Mura, Grimm.
3. Undetermined: Manson.

B. *Infection:*
1. (*a*) Bacterial (definite): Pekelharing and Winkler, Sangerfield, Durham, Rost, Van Elcke, Okato and Kokubo, Musso and Morelli, Taylor, Wright, Wheate.
   (*b*) Bacterial theory but not any recognized *one:* Manson, Castellani, Arnold, Baelz, MacGilchrist, Stanley, Daniels, Pearse, Lovering, Schubert, Balz, Legendre, Lovelace, Scheube, Shibayama, Marchoux, Travers.
2. Protozoan: Glogner and Heavley, Hewlett and de Koste, Fajardo.
3. Nematodes: Noc Kynsey.
4. Fungi: Rose.

C. *Deficiency in Diet:*
Phosphorus: Schaumann, Aron.
Nitrogen: Takaki.
Potassium: Fales (and green vegetables).
Proteins and fat: Van Leent.
Poorly balanced, monotonous and inefficient diet: Vordermann, Braddon, Fraser and Stanley, Eijkman, Grijns, Highet, Nocht, Woolley, Chamberlain and Vedder,[1] Strong and Crowell, Heiser, Kilbourne, Hunter and Koch, Holst, Frohlich, Herzog, Gimlette, De Haan, Little, Darling,[1] Funk,[1] Williams,[1] Gibson.[1]

[1] Specific vitamine.

As indicated, beriberi occurs for the most part in tropical countries, and the classification given above indicates that practically all the theories that have been advanced recognize that the disease depends on the nature of ingested material. This is true whether the ingested material be harmful through insufficiency, through intrinsic poisonous properties or through forming favorable conditions for the development or growth of harmful material in the intestines. Almost all of the champions of the bacterial origin of the disease, among whom Wright holds a prominent place, consider the alimentary tract to be the portal of entry. Wright does consider wound infection a possibility and Manson doubts that it is a food infection.

Aside from those who have described definite microörganisms as the cause of the disease there are others who believe that bacteria, protozoa or fungi may produce changes in the food before consumption, and those who favor the idea that the food forms a favorable medium for the growth of organisms either before or after ingestion.

Concerning the theories which consider inorganic chemical poisons as etiologic factors in this disease, it may be said that very little evidence in their favor has been deduced; they do not furnish a satisfactory explanation of the clinical or pathologic phenomena of the disease, and they have met with no general acceptance among workers on this subject. The same may be said of the theory of ichthyotoxismus and lathyrism.

Infectious Theory. Among the workers favoring the infectious theory there may be said to be two classes:

First among these are the ones who claim to have isolated organisms to which they have assigned an etiologic role; these may be dismissed from consideration at the present time, as none of their work has been confirmed or generally accepted.

The second class is an important one and includes those who, from a study of the epidemiology, symptomatology and pathology of the disease, consider that it is best explained by an infectious theory without themselves indicating any special organism as the one at fault. Their reasoning is largely by analogy with known infectious diseases. In a long list this group includes the names of such distinguished workers as Manson, Scheube, Wright and others.

Manson believes that the disease is caused by the introduction by inhalation or otherwise of a toxin generated by some germ without the body. This germ, he believes, may be carried by man from place to place. He considers beriberi especially a place disease.

Scheube's reasons for considering beriberi an infectious disease may be briefly summarized by stating his emphasis on its occurrence in strong, well-nourished young persons, its geographic restrictions,

its seasonal occurrence, and on his belief that it cannot depend on deficient nutrition.

Wright drew attention to and emphasized the changes in the stomach and duodenum, and he maintained that these are the seat of growth of an organism which produces an extracellular diffusible toxin, and this causes the lesions and symptoms of the disease.

Those theories which ascribed an etiologic role to nematode parasites have never been given serious consideration. A protozoan cause has never been proved, although protozoa have been found by some to be associated with the disease.

Diet. From the earliest time a relation has been noted between diet and beriberi. In the search for the true cause almost every conceivable relation between diet and the disease has been investigated. Especially has its relation to the consumption of rice occupied an important place in the history. In turn, workers have considered the chemical constituents of the varieties of rice, the time and degree of its decortication, the time and manner of its curing and preparation for consumption, the way in which it is stored, the length of time it is stored, the changes occurring in it while stored, and the amount eaten.

The names of Eijkman, Vordermann, Grijms, Braddon, Fraser and Stanton, Heiser, Strong and Crowell, Highet, Chamberlain and Vedder and Funk and some Japanese workers should especially be associated with the growth of knowledge concerning the relation of diet to beriberi. (Omission of names from this list is not intended to belittle the value of an investigator's work, but the list obviously has grown too large to be given complete.)

Some of the ways in which diet has been conceived to be related to the disease are indicated above. The theory which now attracts most attention and seems most plausible is that which regards highly polished rice as an exclusive or almost exclusive article of diet to be deficient in a substance or substances necessary for metabolism. The first step toward the proof of this theory was to establish the fact that the consumption of decorticated rice was followed by beriberi. This has been proved experimentally in man by Fraser and Stanton and by Strong and Crowell. It has also been shown by others on larger scales, as by Braddon, by Vordermann and by Heiser in Bilibid Prison and in the Culion Leper Colony, where substitution of partly decorticated rice for completely decorticated rice led to the practical disappearance of beriberi.

Animal experimentation also has been of great value in advancing our knowledge of this disease. Eijkman in Java noticed the development of polyneuritis gallinarum in fowels fed on decorticated rice, and this work was soon confirmed by Grijns and others. The similarity between polyneuritis gallinarum and human beri-

beri was noted, and much fruitless discussion has been waged concerning their identity. It is sufficient to consider the two conditions analogous and apply truths elicited from a study of the fowl disease to man with caution. In this way it has been found possible to further our knowledge concerning the cause, prevention and treatment of the disease. It has been shown that fowls fed on fully decorticated rice develop polyneuritis, whereas those fed on slightly decorticated rice do not. From this the idea arose that a neuritis-preventing principle is present in the husk of the rice. It has been found, especially by the United States Army Board for the study of tropical diseases as they exist in the Philippines, that extracts of this husk (so-called rice-polishings; in Tagalog tiqui-tiqui) if given with decorticated rice will prevent the onset of the disease or cure it when present in fowl. This extract has also been found of value in the treatment of human beriberi, especially in the infantile form. Attempts at further purification of the neuritis-preventing principle have been made by Funk, Vedder and Williams, Edie and his co-workers, and Susuki, Shimamura and Odake. These workers have obtained substances with different chemical formulæ, so that it cannot be considered that the essential principle has been identified. Funk has given the name "vitamine" to the hypothetic substance which constitutes the neuritis-preventing principle. This had previously been shown to be alcohol-soluble by Chamberlain and Vedder.

Other articles of diet available to the poor in beriberi zones have been analyzed and tested as to their content of neuritis-preventing principles, and with great and often surprising variations. Furthermore, the nature and importance of "vitamines" in diseases other than neuritis have developed rapidly, and new facts that may be of value in the study of beriberi are being accumulated in many places.

Pathology. The condition of the general nutrition of the beriberi patient varies with the stage of the disease and possibly with its type. In the early stage the general nutrition may be good, while in the protracted case marked emaciatiom may occur. Attention has been drawn to the fact that in the so-called "wet" type of the disease the anasarca may conceal a poor state of general nutrition. It must also be noted that a good general state of nutrition may not indicate well-nourished nervous tissues.

Edema. All of the tissues may show a marked edema, and this is manifest by subcutaneous edema which may be widespread, or, in the early stages, confined to the lower extremities, by ascites, hydrothorax, hydropericardium, meningeal and pulmonary edema. Numerous explanations have been offered for the edema. It appears early in the disease and obviously before any renal or cardiac insufficiency is demonstrable. It also occurs in cases in which the anemia is insufficient to account for it. Degenerations

in the *nervi vasorum* have been demonstrated as well as degenerate muscular and intimal changes in the vessels. It seems probable that the edema is to be accounted for by some pathologic change in the vessel walls.

Heart. Hydropericardium may be relatively greater than transudation into the serous sacs, or at times may not be present at all. Herzog found hydropericardium present in 66 per cent of 256 cases collected from the literature. Epicardial ecchymoses are almost always present. Enlargement of the heart is the rule. In the acute pernicious type this enlargement is due to dilatation, especially of the right chambers. In the more chronic cases hypertrophy also occurs and the hypertrophy of the right ventricle is characteristic. Left-side hypertrophy may also occur, but is much rarer. A groove can usually be seen at the apex between the two ventricles. The heart muscle shows parenchymatous degeneration and edema, and may show fatty change. Fragmentation of the muscle fibres and hyaline degeneration have also been described. Nagayo has seen hyaline and fatty degeneration involving the bundle of His. Scheube, Balz, Pekelharing and Winkler have described small myocarditic foci such as are found in diphtheria and other infectious diseases. Scheube has seen cellular infiltration in the subepicardial tissues and small hemorrhages in the heart muscle and beneath the endocardium. Explanation of the cardiac hypertrophy, and especially its usual restriction to the right ventricle, is difficult. Most arguments advanced in explanation in no way elucidate it. Matzuoka's theory appears to us the best, namely, that it is dependent upon the congestion-edema of the lungs. The origin of the pulmonary edema has already been referred to as due to changes in the pulmonary vessels. Degeneration of the intramural cardiac nerves also occurs.

Lungs. Transudation into the pleural sac occurs, but is usually not extensive. The lungs show congestion and edema, usually most marked in the lower lobes. This may be sufficient to lead to splenization. Emphysema of the apical portions and free anterior margin is not uncommon. Aspiration bronchopneumonia sometimes occurs.

Liver. Congestion of the liver forms a part of the general visceral congestion and may advance sufficiently to give the nutmeg appearance. Parenchymatous and fatty degeneration occur as sequels of the congestion. Nagayo has described an excess of glycogen in the liver.

Spleen. No characteristic changes occur in the spleen in beriberi other than those due to passive congestion. The markedly enlarged spleens which have been described in beriberi are undoubtedly due to other causes.

Kidneys. These organs show the effects of passive congestion and parenchymatous degeneration. Fatty degeneration also sometimes occurs. A glomerulonephritis has been described in beriberi by Miura, but it is a fact that the kidneys in this disease show relatively slight changes, and these changes do not account for the edema. Other symptoms of renal insufficiency, such as albuminuria, are not the rule in beriberi.

Stomach and Intestine. Wright drew attention to and emphasized the changes occurring in the stomach and intestine. He says: "The stomach and duodenum are toneless, dilated and empty. Their mucosa is deeply congested, rugæ and valvulæ are flattened and present numerous small hemorrhagic injections. Rings and patches of brilliant congestion occur and prove to be markedly dilated capillaries. They suggest sprinklings of red pepper. This congestion and ingestion may be found as low as the cecum; in a few instances I have found it in the ascending colon. As a rule it is most marked and occasionally wholly confined to the pylorus and duodenum. A thin pellicle of treacle-like mucous has occasionally to be stripped from the congested mucosa, but no true membrane is ever formed. Infrequently the congestion proceeds to hemorrhagic erosion of the gastroduodenal mucosa. The first chain of mesenteric glands is usually swollen. Microscopically the gastrointestinal mucosa exhibits all the signs of an acute inflammatory process." Here it is that he found his Gram-positive bacillus to which he ascribed an etiologic role. In his cases of beriberi residual paralysis he says, "The stomach and small gut are generally slightly dilated, but there is a complete absence of the gastroduodenitis seen in the acute stage of the disease."

In addition to the changes described by Wright, we have found frequently in the acute cases a very marked edema of the mucosa of the stomach and upper part of the small intestine. Intestinal parasites, to which an etiologic role has been assigned by some, have been no more frequent in our cases than in a similar class of patients suffering from other diseases.

Adrenals. Nagayo has described a progressive hypertrophy of the medulla of the adrenals in beriberi. In some of our cases a relative prominence of the adrenal medulla has been noted, but this has not been found as a constant feature.

Thymus. Nagayo has also noted enlargement of the thymus in beriberi. Funk and Douglas maintained that among the changes which take place in pigeons suffering from polyneuritis as a result of an exclusive white-rice diet a marked diminution in size occurs in the glands of internal secretion. His most marked change was in the disappearance of the thymus; macroscopically no thymus could be seen in any of the pigeons with polyneuritis. Following these observations a theory that a severe change in the glands of internal secretion occurs in beriberi has been proposed by Funk

on the *a priori* ground that the vitamines of the food have a close relationship to the glands of internal secretion. Williams and Crowell concluded on experimental evidence that there is no fundamental connection between beriberi and atrophy of the thymus, and that when the latter occurs in birds fed on polished rice, as it frequently does, it is due to some other cause. So in our autopsy records of adult beriberi humans it is found that the thymus gland is usually small. Crowell has already drawn attention to the occurrence of enlarged thymus in some cases of infantile beriberi and its association with status thymicolymphaticus.

Pancreas. No change in the pancreas has been described as characteristic of beriberi.

Lymphatic Tissue. Nagayo notes the enlargement of the lymphatic apparatus and classifies it as a progressive (restorative) change. He says that the changes in the lymphatic tissues may be due to a poison. The lymphatic tissues of the body have been especially noted by us in our autopsy work, and no change in them has been found in beriberi unless associated with other stigmata of status thymicolymphaticus. We see no evidence which points to any unusual incidence of status thymicolymphaticus in beriberi.

Muscles. Beriberi has been defined as a neuromuscular degeneration. Following, or coincident with, the nerve degeneration there occur fatty, hyaline and colloid degeneration of the skeletal muscles. The muscle fibers become thin, lose their striation, become homogeneous and fragmented. Cellular infiltration and hemorrhages between and into the muscle bundles have been described. Marked atrophy of the muscles follows, with replacement of the muscle fibers by fibrous connective tissue.

Nervous System. To Scheube and Balz belong the credit of demonstrating for the first time that the essential lesion in beriberi is a degeneration of the peripheral nerves. The degeneration may be present in the central nervous system, but is most prominent in the peripheral nerves. According to Scheube, sensory and motor nerves to the muscles are most affected in the dry or atrophic form of the disease, vasomotor nerves in the wet or hydropic form and the vagi in the acute pernicious types of the disease. The nerve endings in the muscles, as well as the nerve stems, are affected. Changes have been described in the vagi and phrenics, in the splanchnics and their visceral branches, in the solar and renal plexuses, in the nervi vasorum, in the cervical sympathetic ganglia, in the cutaneous nerves and in the nerves of the extremities. The changes occurring in the peripheral nerves do not seem to us different in type from those occurring as the result of various organic and inorganic poisons, such as in diphtheria and typhoid and in alcohol, arsenic and lead-poisonings.

According to Scheube the most severe changes are in the muscle branches of the nerves, and the main nerves show slighter changes.

In general, he believes the grade of degeneration corresponds with the paralytic symptoms, the most severe changes occurring in the chronic cases, while acute cases may even die before degenerative changes are demonstrable. It has been held by some that the process originates in the peripheral nerve endings and extends centripetally, but this requires demonstration.

The change that occurs in the nerve is first a degeneration of the myelin sheath with its conversion into a fat-like substance that stains black with osmic acid. Within the neurilemma are seen globules of this degenerated myelin which may distend the neurilemma and give a beaded appearance to the nerve. At other places these globules are smaller and the neurilemma is not filled. The globules may be vacuolated and foamy in appearance or a long area of the myelin sheath may appear uniformly black and wavy after osmic impregnation. The degeneration is accompanied by a fragmentation of the axis-cylinder, which in appropriately stained preparation may be seen in comma-shaped or S-shaped fragments within the masses of degenerated myelin. Eventually the neurilemma sheath may entirely collapse and it may show a multiplication of nuclei which is interpreted as an effort toward regeneration of the axis-cylinder. Degeneration fibers in a nerve may be very numerous, or only a few may be seen in the small part of the nerve usually submitted to examination, while the other fibers appear intact. Durck has demonstrated tyrolysis and vacuolation of the ganglia cells in the anterior horns of the spinal cord and in the spinal ganglia.

Degenerations have also been described in the fibers of the columns of Goll, Burdach and Clarke in the nuclei of the funiculus gracilis and funiculus cuneatus. According to Wright the cells of the bulbar nuclei and the nucleus ambiguus on both sides are swollen, with excentrically placed nuclei and a massing of the tigroid bodies.

Degenerative changes have also been demonstrated in the intrinsic ganglia of the heart, in the vagal nerve endings and in the nerve endings in other viscera.

Special attention has been drawn by Japanese authors to the degenerative changes in the nerves in the vessel walls. In the meninges congestion is the rule and small hemorrhages may occur.

Symptomatology. The clinical manifestations may be best understood by classifying them under four varieties:

1. Usual type.
2. Severe fulminant or pernicious type.
3. Chronic type and residual conditions.

Usual Type. The onset usually is somewhat insidious. The patient complains of a general feeling of discomfort or, as sometimes expressed, feels toxic. There is more or less epigastric distress which varies from a sense of fulness and indigestion to more

or less actual pain. The patient tires easily and there may be headache of a dull, heavy character. This prodromal stage may last from one to two or three days. Frequently the disease seems to be brought out during some slight indisposition, such as a "cold," diarrhea, slight fever or fatigue from prolonged exertion. In these circumstances there are no prodromal symptoms which may be positively charged to the neuritis. In any case the symptoms characteristic of the disease develop quite rapidly, so that the typical clinical picture is established within two or three days, although it may be delayed for a week. In the order of development the symptoms do not follow a fixed rule. Usually, heaviness, numbness and more or less pain develop in the legs. This is noticeable on walking, from which the patient quickly tires. Numbness and paresthesias develop first in the calf muscles, to be followed by pain on motion and tenderness on pressure. Edema, noticeable first as slight pitting over the lower tibia, progresses gradually over the legs and feet and later in other parts of the body, particularly the hands and face.

Usually the epigastric symptoms are considered to be indigestion, and, as a matter of fact, this frequently is the complaint which takes the patient to a physician.

As the disease progresses the leg pains become decided, particularly on motion or pressure; the joints feel as if they were out of control; the numbness may extend to the hands, arms and face; the edema becomes noticeable in the face and hands; a general sense of depression and oppression is complained of and the gait becomes characteristic of the disease. The altered gait is principally characteristic in that it is neither ataxic nor spastic, but more a combination of the two, and within a few days the patient is no longer able to walk or to stand without assistance.

The patellar reflexes at the very beginning frequently show a transient period of increased excitability, but they quickly become markedly diminished and finally lost entirely. The superficial reflexes usually remain normal.

In the fully developed disease the patient stays in a fixed position because motion increases the pain; the face and more or less rapid respiration indicate embarrassed circulation. The facies in general are those of an ill patient, the skin varying from normal to more or less cyanosis, the face, legs, feet, hands and frequently other parts of the body showing more or less edema; respiration and pulse are accelerated. There is epigastric distress, pains and tenderness in the legs and sometimes in the upper extremities. Numbness and paresthesias are unevenly distributed and more extensive than the pain areas.

The secretion of urine is diminished and there not infrequently is some looseness of the bowels. Nausea and even vomiting may be present.

Examination of a patient at this time shows tachycardia due to myocardial changes and influenced in some cases by more or less fluid in the pericardial sac. The rapid respiration may be due to embarrassed circulation, or there may be some fluid in the pleural cavities, and there may be a cough with considerable fluid expectoration.

There is tenderness over nerve areas, more marked in the calves, and usually pain is much increased on motion of the lower extremities. The patellar reflexes are absent. There is nothing significant to be found by examination of the urine or blood.

The patient may continue in this condition for days or weeks, with but slight change. In fatal cases the symptoms get worse, the pulse increases in rate, the edema extends, more fluid is found in the serous cavities and the patient finally succumbs to cardiac failure, less frequently to paralysis of respiration, or sometimes to acute pulmonary edema.

In patients who recover, the symptoms subside slowly, frequently but not invariably in reverse order to their appearance. As the circulation improves and the edema subsides the enormous muscle-wasting becomes apparent. Convalescence is exceedingly slow, lasting frequently for many months, and sometimes complete restoration of function never is attained.

There may be considerable variation in the clinical picture even in what we have termed the usual type. All of the symptoms may not be present in a given patient, and the order of their appearance may vary also. In one patient the epigastric symptoms may be the most pronounced and annoying, in another the cardiac symptoms may predominate, and there is frequent and marked variation in the extent and amount of the edema. In fact the edema may be so slight and temporary that the "dry" stage may be considered to be primary. Some authors consider that the dry form does develop primarily without there ever having been edema. However the matter is not considered one requiring lengthy discussion.

Severe, Fulminant or Pernicious Type. This type differs from the former chiefly in the intensity of the disease and the early and fatal heart failure. The onset usually is sudden. The whole cycle of the disease may be completed within one day, although the average duration is two to five days. It may develop out of a previously milder case.

This type of beriberi is a veritable plague, with very acute symptoms, a rapid course and practically always fatal. It rarely is encountered sporadically but occurs in prisons and in overcrowded places where the disease is epidemic. The nature of the symptoms and the order of their appearance frequently is much the same as in the usual type, but much intensified. The circulatory symptoms are the striking and characteristic features. They appear early and are the first and sometimes practically the only ones

present. At first there is tachycardia followed by increased respiratory rate, cyanosis, rapid heart failure and death. Edema of the lungs may constitute the terminal condition.

From first to last the clinical picture may not be distinguishable from that of acute progressive heart failure due to myocardial insufficiency from other causes. The expression is anxious, skin moist, eyes staring and pupils dilated, heaving chest motion and diffuse palpatory thrills.

Epigastric distress with vomiting is an early, severe and constant symptom. When the disease is a little less malignant and patients live more than two or three days the clinical picture may approach more nearly that given for the usual type. The edema has time to develop and the clearer intelligence allows a keener appreciation of pain and other subjective symptoms. The accumulation of fluid in the serous cavities is noticeable, the urine diminished, and there is thirst and loss of appetite.

Mild or Rudimentary Type. The onset is insidious. The earliest symptoms consist in a feeling of languor, a dull, stuffed sensation in the epigastrium, heaviness, numbness and some tingling about the calves. The sensations in the legs frequently are more noticeable in the night or early morning, particularly during the cooler season, when after hot days there is quite a decided chill in the early morning hours. Examination of a patient at this time will reveal slight but definite tenderness of the calves, slightly exaggerated but more generally definitely diminished patellar reflexes and possibly some acceleration of the heart-beat. In the majority of instances the patient will show slight but definite disturbance in the gait, consisting of hesitation in lifting the foot and an uncertainty or delicacy or deliberateness in placing it on the ground again.

One rarely sees this stage in hospital or private practice, but in the outpatient clinics for the poor it is encountered with great frequency. Unless the disease advances beyond this point there may be a question as to whether or not it really is beriberi. Most of these patients are from teamsters, laborers, rice-workers and others whose occupation keeps them outside, and they attribute the condition to getting wet suddenly while being exposed to the heat.

As the disease progresses the pains in the muscles of the legs, particularly the calf muscles, become more pronounced. These pains are spasmodic—cramps—and during the intervals between pains paresthesias are more or less constant. There is often a constant soreness of the mucles, and weakness of the legs is complained of after a few days or weeks of the disease. Other symptoms are dizziness, increased by exposure to the sun or by close application of any kind; slight epigastric distress and frequently some slight nausea. *Objectively* not much is found. The calf muscles

and often other muscles are tender on pressure and the patellar reflexes are sluggish and sometimes absent. Edema is slight or absent and examination of the heart may be negative. The blood, urine and feces do not show anything definite.

The disease lasts from a few weeks to months and even years unless treatment is instituted. Under rest in bed or confinement to the house, appropriate food and a simple bitter tonic recovery is rapid. Apparently one attack does not confer immunity, but rather seems to increase the patient's susceptibility. We have seen the same patient with as many as three attacks in one year.

During the protracted period of invalidism the patients hobble about, eke out an existence in various ways and alternate in "cures."

Muscular spasms and cramps of the legs with some paresthesia, noted more during cool nights, is not by any means confined to the Orientals. Many Occidentals who have resided in the tropics for years are sufferers from it. In many instances the exceedingly mild condition takes on other symptoms which are definite and leave no doubt of the diagnosis of a neuritis.

Chronicity and Residual Conditions. Except in the acute fulminant type the natural tendency of beriberi is toward chronicity. It is primarily a long-drawn out, slow-acting process, with acute exacerbations and tedious recovery, blending often into residual conditions which may be permanent and always disappear very slowly.

Regardless of the manner of the onset and the presence or absence of edema we have in the chronic beriberics a large problem. The extent of incapacity varies from those slightly crippled with leg cramps and tachycardia on exertion to completely helpless invalids, emaciated and miserable with pain.

After all activities of disease have subsided the residual paralysis, muscle atrophy and cardiac hypertrophy and dilatation remain for long periods of time, and it not infrequently happens that complete restoration of form and function never takes place.

Analysis of Symptoms. *Gait.* The gait is characteristic principally in that it differs from the various ataxias and spastic gaits of well-known diseases. It differs somewhat in accordance with the nerves involved, and consequently the corresponding varieties of muscle atrophy. True ataxia is never seen, but a spastic gait resembling that of spastic spinal paralysis may occur during convalescence.

Disturbances of Motor Function. All stages of muscular inefficiency are encountered, from numbness and sluggish action in mild cases to complete paralysis in the severe prolonged cases. There is selectiveness and variety in muscular involvement corresponding exactly to the distribution of affected nerves. In the order of frequency the muscles of the feet, legs, hands and arms are involved. Beyond various muscles of the face and body those

of most importance and serious consequence being the diaphragm and heart muscles. The sphincters are not involved. The electric reactions are similar to those found in peripheral neuritis due to other causes.

Vasomotor and Sensory Changes. Paresthesias of many types and varying form from complete anesthesia to the most intense hyperesthesia always form a part of the clinical picture. Those most prevalent are localized anesthetic areas corresponding to the anatomic areas most involved in the disease. The lips and tongue are paresthetic, frequently without signs of muscular insufficiency. The physical conditions of cold, moisture, pressure, etc., that affect paresthetic areas apply here. In interpreting phenomena of anesthesia and paresthesia it is well to remember that usually our patients are among the most ignorant natives of the tropics, who appear to be less responsive to our ordinary testing methods, and unless care is used errors are liable, particularly in interpreting anesthesia.

Vasomotor dilatation of the superficial vessels of the skin may lead to the most pronounced perspiration, and rarely an erythematous blush in affected areas may be seen among the lighter-skinned patients.

Alterations in Reflexes. The patellar reflex may be increased for a brief period at the onset of the disease. In all established cases it is either decidedly diminished or more frequently entirely absent. Altered patellar reflex usually is one of the earliest symptoms to appear and among the last to be restored to normal after recovery from the disease.

Circulatory Disturbances. Tachycardia in varying degrees is a constant symptom. In mild cases it may be scarcely noticeable on resting and only shows an exaggerated reaction from the mildest exercise. In more severe cases it becomes a prominent symptom, justly causing great anxiety to the patient, who can feel the increased rate and labored action of the heart. Frequently there is precordial pain. The heart symptoms are due to myocardial changes, with dilatation more marked on the right side but later involving both ventricles.

Edema and the collection of fluid in the serous cavities to a greater or less extent occurs in most cases of the disease at one time or another.

It is not unlikely that the transudation and exudation are dependent upon some more or less definite factor in the course of the disease as yet unknown. The frequent presence of dry atrophy as opposed to edema may be a striking symptom throughout the course of the disease. The more or less complete transfer from "wet" to "dry" varieties in the same patient is not easily explained, except by assuming an as yet unknown influence in the etiology of the disease.

The accumulation of fluid in the pericardium or pleural cavity may be sufficient in quantity to cause serious consequences. The amount in the abdomen and elsewhere is smaller, but there usually is some in all serous cavities, at least in acute cases of the disease. The edema usually appears first in the feet and legs, hands and arms, then the face, and later in severe cases one sees a striking picture of general anasarca. Pulmonary edema is not an unusual form of termination of the acute disease.

Fever is not a symptom of beriberi, and when present is due to some associated condition.

The systolic *blood-pressure* is generally lower in the tropics, both among natives and foreign residents, than it is in temperate climates. Even taking this fact into consideration the records seem to show that beriberi produces a lowering in the systolic pressure. This was true in the experimental cases of the disease studied by Strong and Crowell.

Blood examinations by the usual laboratory methods show nothing characteristic of beriberi. What departures from normal there are may be explained by associated conditions. A number of writers have called attention to a relative mononuclear increase of varying degrees, but Chamberlain and Vedder and others have shown that the relative increase in the lymphocytes is a pretty general condition in the tropics.

Alimentary System. Epigastric discomfort or distress is frequently an early symptom—sometimes the very earliest in the disease. These symptoms are probably due in part to more or less disturbances in the duodenum and in part to interference with digestion. They may be entirely absent. Nausea and vomiting may be distressing symptoms in fulminant cases and are fairly frequent in less serious forms. Diarrhea and other symptoms of intestinal disturbances are not important.

Urinary System. The most important symptoms are the variations in the quantity of urine excreted. Frequently in severe types the quantity is much decreased, and it may cease altogether before death. At times in the dropsical form there may be a very marked increase in the quantity of the urine, a change usually simultaneous with the reabsorption of fluid from the edematous areas. There are no characteristic changes found in the urine on routine examination.

Diagnosis. In endemic zones there is usually no particular difficulty in arriving at a diagnosis of multiple neuritis. Unfortunately only too often the diagnosis of neuritis is accepted as synonymous with beriberi. The differentiation between beriberi and multiple neuritis of other etiology is not easy to make by direct examination, and is only justified after a painstaking and thorough investigation into the etiology of each case.

Beriberi is most frequently confounded perhaps with alcoholic

neuritis. This mistake is made easy by the unfortunate statement so frequently seen that Orientals do not take alcohol. There is no greater fallacy in print. The poor people consume very poor qualties of cheap spirits, gin or beer, and in addition different localities have many different crude methods of preparing alcoholic drinks.

Differentiation from various other cropsies and edemas ordinarily is not difficult. However, it seems advisable to call attention to the mechanical difficulties encountered in examining the reflexes in patients already with much edema, particularly of the legs.

Prognosis. The mortality rates, as in all other pandemic and epidemic diseases, vary greatly as reported from different countries, as well as from different localities in the same country. The mild form rarely is fatal, but it often changes, and quickly, to a more severe one with higher mortality, and this potential danger must be recognized. The acute fulminant type is practically always fatal. Mortality in the usual form varies from 2 per cent to 60 per cent as given by different authors and representing statistics from different endemic zones.

Preventive Measures. Whether considered from a public health, social or medical standpoint the prevention of tropical neuritis is a large and urgent problem. More than half the population of the world live within the endemic zone and the disease must be eliminated before great permanent progress will be made in the development of many countries.

Beriberi is essentially a disease associated with ignorance, squalor and poverty. The home *par excellence* of these conditions, and therefore the home of beriberi, is in the tropical and subtropical belts, with its hundreds of millions of ignorant, superstitious, poverty-stricken people who live in tropical filth and lead a hand-to-mouth existence without thought or care for the morrow, and only too frequently where efforts at improvement are received apathetically or are resented.

The task of providing the essential remedies of better homes, better food and cleaner living is a disheartening one. Temporary improvement may be achieved in local areas by organized government and other charities, but this further pauperizes the people and is an impossible permanent solution on a large scale from an economic standpoint. Compulsory control over the lives and activities of the people has been employed in places. It is an effort of doubtful utility and one certainly not free from danger. Permanent results may be achieved only by instilling the attributes of thrift, energy, cleanliness and physical development into the people. To do this would include the expenditure of large sums of money; require a firm, non-political government and the constant directing influence of skilled advice over a period of several generations. The energetic, thrifty, clean-living citizen is at present

a tropical exotic, and the propagation of a population of this class is unlikely. Certain things, however, may be done, and the most important is to secure by the best and most practical means applicable to any given community such improvement in the food supply as is possible. This may be done, as in the Philippine Islands, by teaching gardening in the public schools and stimulating the cooking and use of good home-grown foods.

There is no doubt but what "undermilled" rice is a safer article of diet than that with all of the pericarp removed, and under circumstances where it is practically the sole available foodstuff for the poor, every possible effort to secure its use should be employed. Enforced use of whole rice may, of course, be employed by the military and in prisons and certain other institutions under such complete control that the inmates have little to say about what they shall do or eat, but compulsion should not be attempted among a people who have a voice in their own affairs. The Philippine experiment illustrates this point: Although red rice is not delectable to a rice lover, it might have been made popular, just as the Bureau of Education made the use of maize popular, except for the great and widespread resentment created by endorsing its exclusive use among soldiers, lepers and prisoners.

Nations holding colonial interests within the endemic zone of tropical neuritis can render no greater service to humanity than by studying their local problems and applying methods that will ensure the universal use of a better and more varied diet than exists in those countries at the present time.

Treatment. The treatment of beriberi is symptomatic and specific. The vast majority of patients are too poor to buy medicines, and when they do succeed it is at the sacrifice of food for themselves and perhaps their children. A clean bed in a light sanitary room and proper food will cure more of these patients than medicine, and it is less expensive. A glass of milk is a better "tonic" than all the drugs in the pharmacopeia.

Among the better-class patients the refined methods of symptomatic treatment may be instituted. The circulatory, urinary and digestive functions should be watched. Strychnin, digitalis, atropin and various other heart stimulants have been recommended to guard against or relieve existing circulatory or respiratory embarrassment. They are of doubtful value. Absolute quiet in bed with an ice-bag over the heart will do much to prevent the necessity of treating urgent heart symptoms. Squills, citrate of potash and other similar remedies are used to relieve the diminution in urine secretion, but are also of doubtful value. Small doses of concentrated solution of magnesium sulphate are indicated when a laxative is necessary.

Specific Remedies. Quite a variety of drugs have had from time to time more or less vogue as specifies. It may be safely stated than none of them has any such properties.

Due largely to the researches of Funk, Vedder, Chamberlain and many others during the last few years, decided progress has been made toward a specific treatment of the disease by the use of appropriate foods and particularly by the use of extract of rice polishings and other substances rich in "vitamines." Some of the reports of the results of this method of treatment have been overly enthusiastic, but definite progress has been made and a sound foundation for further investigation established.

The extremely grave and widespread infantile type of beriberi (taon and many other local names), as well as the multiple neuritis of pregnant and parturient women, constitutes one of the most interesting and baffling problems in tropical neuritis, which may have consideration in a subsequent article.

CLINICAL DIFFERENTIATION OF EPIDEMIC ENCEPHALITIS, ACUTE POLIOMYELITIS, BOTULISM AND CERTAIN FORMS OF FOOD AND DRUG POISONING.

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Epidemic encephalitis, botulism, certain forms of acute poliomyelitis and cerebrospinal syphilis, wood-alcohol poisoning and poisoning by drugs, such as veronal and members of the belladonna group present in common involvement of the cranial nerves resulting frequently in considerable diagnostic difficulty. It is the purpose of this paper to present a comparison of the various points which may be used in differential diagnosis of these conditions.

Poliomyelitis (Acute Poliomyelitis, Polioencephalitis, Infantile Paralysis or Heine-Medin's Disease) was first described by Jörg in 1816, who noted the occurrence of a febrile disease followed by paralysis of the limbs and subsequent club-foot. It is hardly necessary at the present moment to review the contributions to the subject of Heine-Medin, Wickman, Peabody, Draper and Dochez, Flexner and Amoss, Webster, Rosenow and many others more than to say that the old conception of the disease as expressed in the term "infantile paralysis" has given way to the recognition of the fact that the disease is a general infection in which paralysis may or may not occur. It is characterized upon an average by an incubation period of variable duration, usually about a week, followed by a stage of prodromal symptoms which are at times slight and of a very transitory nature and easily overlooked, then an acute stage with paralytic manifestations and lastly a period of retrogression. The prodromal symptoms are of a very general nature and vary from epidemic to epidemic. They may be so

slight as to be entirely overlooked, and the first indication of the presence of the disease is then a paralysis. Undoubtedly the most constant and important symptom of this period is fever of an irregular character varying from a slight rise to 103° F. or more. Initial chills are infrequent. Profuse sweating has been noted by Müller in 75 per cent of his cases; other observers failed to notice any sweating in more than 25 per cent. It is evident that this symptom varies considerably. Drowsiness of varying duration and intensity may be present; the patient, however, may be easily aroused, but is usually found to be then irritable to a considerable degree. This irritability manifests itself in an expression of fear of being moved or examined, and is associated with another cardinal symptom, hyperesthesia of the skin and pain on passive motion, specially those motions which cause anterior flexion of the spine—or the legs at the hip-joint and forward bending of the neck. While retraction of the head is not often seen, there is, nevertheless, a tendency of the head to fall back when the child is lifted from the bed by the hands, and there may be found a stiffness of the posterior neck muscles. Test for Kernig's sign results in pain and resistance of the hamstring muscles. These pains and stiffened muscles are a result of meningeal irritation which occurs in the preparalytic stage. Before paralysis takes place there may also be a definite weakness of various groups of muscles, as seen in walking or standing. While convulsions are quite unusual, muscular twitchings are rather frequently seen.

The onset of the disease may be manifested by involvement of the respiratory tract as seen in an inflammatory reaction of the conjunctiva, nose, throat, bronchi or lungs. Regan describes at length the mouth and throat findings in his series of cases, and calls attention to congestion of the throat as an almost constant symptom in the early acute stage accompanied by a varying degree of capillary enlargement on the faucial mucosa and pharynx. The palate, pillars and uvula are a diffused deep red, the soft palate a deep red with distinct purple or violaceous tinge; the hard palate pink—the more severe the deeper the color. In the severe bulbar types in which the prognosis is bad there may be an anemic appearance of the throat. A mild tonsillitis he finds constant. There is never a membrane but spots similar to Koplik's spots sometimes are seen. The tongue is heavily covered with a grayish or white coating, usually moist, and the tip and edges uncovered and slightly redder than normal. The covering is absent in some places, so that the red shows through. The five most important signs of meningeal invasion are: Neck stiffness with weakness of the anterior neck muscles; unwonted drowsiness; hyperesthesia; ataxic gait and sometimes muscle twitchings. The first two combined are almost pathognomonic. In the bulbar type the child may be extraordinarily acute or stuporous. Constipation is

usually present and also anorexia. Urinary retention may occur during the fever; diarrhea with green mucous stools may be a predominating feature. Vasomotor disturbances, such as flushing of one ear or cheek, may occur. The spinal fluid usually is abnormal —it may be clear or slightly opalescent, under increased pressure, increased cell content and increased protein. If the clinical picture be considered with the spinal-fluid findings it may be possible to make a diagnosis in the prodromal stage. When paralysis occurs the diagnosis offers less difficulty.

Paralytic Stage. The paralysis may be considered from an anatomic point of view as follows: Spinal paralysis; paralysis of the diaphragm; paralysis of the intercostal muscles; paralysis of the abdominal muscles; paralysis of the neck and back muscles; bulbospinal paralysis and rapidly progressive fatal cases presenting the symptom-complex of Landry's ascending paralysis, in which death ensues from paralysis of the respiratory organs.

The spinal paralyses present no special difficulty in diagnosis; in the great majority of cases muscles of one or both legs are paralyzed and in nearly one-half of the cases the paralysis is limited to the legs. Owing to the fact that the phrenic nerve has a large number of roots originating from the 3d, 4th and 5th cervical segments, paralysis of the diaphragm is comparatively rare, although in fatal cases it is usually present, being preceded, however, by paralysis of the intercostal muscles. Paralysis of the abdominal muscles may take place and is usually difficult of recognition. It is necessary to remember that paralysis of the neck and back muscles may occur. In the former it is impossible for a patient to support the head, which falls helplessly in one direction or another. While this condition may resemble the paralysis seen in botulism, the differentiation, as a rule, presents no difficulties, as in cases of poliomyelitis in which there is paralysis of the neck and back. There is generally, also, extensive paralysis of both arms and legs. The same may be said of most instances of combined spinal and bulbar paralysis which are associated with extensive lesions involving the arms and legs as well as the muscles supplied from the medulla. However, bulbar paralysis may occur without the association of spinal paralysis. The facial nerve is the one most often affected either in whole or in part. Palsies of the ocular muscles, specially the abducens, have been noted, sometimes extensive involvement of the eye muscles and even ophthalmoplegia externa; nystagmus is rare; involvement of the optic nerve practically never occurs; phonation and speech may be interfered with and swallowing is sometimes difficult. The tongue may be protruded to one side, or there may be bilateral involvement with inability to protrude the tongue at all. When bulbar paralyses occur in conjunction with spinal paralyses they are much less apt to be severe or lasting than when they occur alone. Associated with

these high lesions is an ataxia of the arms and legs with exaggeration of the knee-jerks and Achilles reflexes and a tendency to stiffness of the legs. Romberg's sign may be markedly present. While the exaggeration of the reflexes may be persistent for a long time the ataxia rapidly disappears.

In the rapidly progressive fatal cases the picture of an ascending paralysis is presented. The mind is usually clear and the patient dies when the diaphragm and the intercostal muscles become involved. Just as the occurrence of paralysis of an arm or leg may be a very sudden manifestation, so also may a sufficient paralysis to cause death occur in a very short time, sometimes within five hours. Ordinarily, however, there is at first a more or less extensive paralysis which involves either the diaphragm or the intercostal muscles followed by an interval of several days, then a slow extension of the paralysis until respiration finally ceases. Fever is always present in the fatal cases, ranging, as a rule, from 101.5° F. to 102.5° F., and sometimes not over 100° F. This occurrence of fever with the onset of the disease is in sharp contradistinction to the subnormal temperature which occurs in the early stages of botulism, fever not being present until a complication such as bronchopneumonia sets in. In both of these conditions, however, the mind is remarkably clear, differing from that seen in encephalitis lethargica. In the bulbar paralyses of poliomyelitis the mouth secretions are not diminished as in botulism, and a frothy saliva fills the mouth and collects between the lips, while in botulism the salivary secretion is diminished, as are all other secretions, and a thick viscid mucous difficult of expulsion fills the throat.

Cerebral Type. Strümpell, in 1885, suggested the name polioencephalitis for a group of cases of cerebral paralysis in children, and pointed out the resemblance to poliomyelitis. The onset of the disease was sudden with a febrile initial phase, vomiting, convulsions and prodromal period, sometimes absent, lasting for two or three days, sometimes over a week, marked by rapid convulsive seizures; after this time the child was found to have a hemiplegia which gradually began to improve. The paralysis was of the upper segment type without atrophy or reaction of degeneration and with exaggerated reflexes. There remained afterward in some of his cases permanent disturbances of cerebral function such as athetosis, epileptic seizures, speech disturbances and diminution of intelligence. He pointed out that, as in poliomyelitis, the lesion was in the gray matter of the cerebrum, the cortex. The final proof that typical cerebral paralyses have the same etiology as poliomyelitis, in which the transference of the virus to monkeys and the causing in them of poliomyelitis has not been accomplished, but both a flaccid and a spastic paralysis have been found in the same patient and a flaccid paralysis in one member

of a family and a spastic paralysis in other members of the same family.

Abortive Types. This is the term applied by Wickman to those cases which show the usual prodromal or preparalytic symptoms, but which do not develop paralysis. These may be cases which run the course of a general infection in which meningeal irritation is specially marked or in which pain is a very marked feature, as in influenza or cases with predominating gastrointestinal disturbances. The serum of these patients acts in the same way that the serum of those who develop paralysis does. It neutralizes the virus *in vitro*, and it is interesting to observe that the serum of a patient who had been paralyzed thirty years before was still able to protect a monkey from the virus of poliomyelitis. Peabody, Draper and Dochez in their monograph point out that it is quite probable that in the past many of the abortive cases have been unrecognized, and in some cases at least the apparent immunity of adults may be due to some previous unrecognized attack.

Epidemic Encephalitis. Epidemic encephalitis, like acute poliomyelitis, is a contagious disease due to a filtrable virus that exists in the nasopharyngeal secretion and in which the nasopharynx serves as a portal of acquisition and dissemination of the disease. While the virus may be preserved for a long period of time in glycerin its virulence is diminished by drying, and while undoubtedly it is usually a droplet-borne disease and propagated directly by the exhalations of the mouth from one person to another, it is, nevertheless, possible that the disease may be carried by insects, such as flies, as is also true of poliomyelitis. Like poliomyelitis also the possibility of convalescent or immune carriers must be considered as a possible and a probable source of the disease. The pathology consists typically of microscopic perivascular lymphocytic infiltrations scattered through the basal ganglia and particularly marked in the brainstem; small hemorrhages may occur, while visceral manifestations have been observed, such as enlargement of the spleen and mesenteric glands and ecchymoses in the pleura, pericardium, bladder and stomach. Visceral changes at autopsy are very inconstant. The blood examination shows nothing characteristic, although a moderate leukocytosis is the rule. The spinal fluid shows little or no change, the fluid is clear; the pressure is not increased; there may or may not be a slight increase of cells (lymphocytes); globulin is usually increased; Lange's colloidal gold test varies. According to Moffitt it may be entirely negative, quite frequently moderately luetic and more rarely an outspoken paretic one. He remarked that the Wassermann reaction is uniformally negative except in complicating cerebrospinal syphilis.

A characteristic feature of epidemic encephalitis is the spread-out course of the occurrence of the symptoms. This is in sharp

contradistinction to the rule in poliomyelitis, in which the entire extent of the paralysis may be accomplished in a few hours or at most in a few days. In one of my cases after an abrupt onset in which there was sudden double vision, gastric disturbances, horizontal and vertical nystagmus, unilateral ptosis, optic neuritis, inability to stand, lasting an hour or two, the patient improved during the course of a week, when a renewal of the symptoms occurred with paralysis of the facial nerve that in its turn disappeared in six or eight days, when suddenly an involvement of the hypoglossal took place with marked deviation of the tongue. One of Moffitt's cases died thirteen months after the onset from a relapse of the same type of the disease she had had at first. Others of his died from twelve days to seven weeks after the onset.

If one remembers the typical lesions of epidemic encephalitis, the small areas of lymphocytic infiltration lying about the blood-vessels and that they may occur in any part of the nervous system, he may more readily understand the varying combinations of symptoms, and if it be assumed that the virus of the disease is active within the patient for a varying period of time, sometimes for many weeks, the cause of the peculiar progression of the occurrence of symptoms will be evident.

If two or more of the cardinal symptoms of the disease occur—that is, a state of lethargy or somnolence, marked asthenia, fever of irregular type and cranial nerve palsies—epidemic encephalitis should be suspected. The suspicion is strengthened if the condition has been preceded by influenza. Fever may be slight and be entirely overlooked. The palsies most frequently involve the ocular muscles; there may be ptosis, more or less complete, strabismus, lateral and vertical nystagmus, pupillary changes, occasionally optic neuritis, all of which may be either unilateral or bilateral. Facial palsies occur, sometimes involving a muscle or small group of muscles, sometimes giving a Parkinsonian mask-like expression to the entire face. Pain, myoclonus and convulsions may occur and meningeal symptoms have been noted as dominating the picture. The pains may be of extreme severity, sharp, localized and extremely intractable; these pains may occur in any part of the body, as a finger, ear, in the abdomen, the teeth, the eye or elsewhere. They frequently precede myoclonus and usually stop when the myoclonic jerking of the muscles begins. Convulsions due undoubtedly to cortical irritation may be the initial symptom or may occur later in the disease. In mild cases somnolence may not be very marked, but, as a rule, lethargy distinguishes it from the mental condition of poliomyelitis or botulism. A varying degree of optic neuritis further distinguishes it from these two conditions.

Botulism. Botulism is a state of intoxication which follows the ingestion of the toxins produced by Bacillus botulinus, either

type A or B. It can be mistaken for methanol poisoning, epidemic encephalitis and cerebrospinal syphilis. Its symptoms usually occur from twelve to twenty-four hours after eating food containing the botulinus toxin, and may be preceded by gastrointestinal disturbances, particularly in the more severe and fatal cases. Symptoms may occur as early as two hours after or may be delayed for two or three days or even longer in making their appearance. One case has been reported nine days after and another as late as fourteen days, but these are indeed unusual.

The symptoms are classified as follows:

1. Arrest of secretions or hypersecretions of saliva and mucous secretions of the mouth and pharynx.

2. Ophthalmoplegia, externa and interna, more or less complete (blepharoptosis, mydriasis paralysis of accommodation, diplopia, strabismus).

3. Dysphagia, aphonia and rebellious constipation, urinary retention.

4. General weakness of all voluntary muscles.

5. Absence of fever and disturbance of sensation and absence of impairment of intelligence.

6. Respiratory difficulties and circulatory troubles, which frequently result fatally more or less rapidly from bulbar paralysis. There is more or less incoördination of muscular movements of the arms and legs, difficulty in picking up small objects, ataxic gait, usually no abnormalities of tendon reflexes.

The patient complains chiefly of double vision, of weakness, of difficulty in walking. There is pronounced difficulty in swallowing and in the expulsion of the thick, viscid, glairy mucus which accumulates in the throat. Agonizing strangling spells resulting in marked cyanosis are of frequent occurrence and often cause death, due to involvement of the respiratory muscles, either intercostals or the diaphragm, or both. There may be a sensation of great weight or pain in the chest and marked difficulty in breathing. The constipation is due to paralysis of the muscles of the wall of the intestines and may resist all efforts to overcome it for quite a number of days. The diagnosis, especially in sporadic cases, may be a matter of considerable difficulty. It may be confused with acute poliomyelitis, but there is an absence of prodromal symptoms, absence of fever, and in by far the greater number of instances of poliomyelitis there occurs definite paralyses of groups of muscles in the extremities. The posterior muscles of the neck in botulism, or indeed all of the muscles of the neck, may be paralyzed, so that the head has a tendency to fall forward. The patient frequently uses his hands to move his head. In poliomyelitis there is a stiffness of the muscles of the back of the neck and a weakness of the anterior muscles, with a tendency for the head to fall backward. There is also a varying degree of

pain on movement in poliomyelitis. In poliomyelitis the mouth secretions are not diminished. The pupils are widely dilated in botulism.

In differentiating botulism from cerebral spinal syphilis the difficulties may be very great, but manifestations of the latter are so generally well known that it is not deemed necessary to more than call attention to the resemblance of the two conditions.

Poisoning by drugs of the belladonna group (belladonna, stramonium, hyoscyamus) show inhibition of secretions and dilation of pupils as occurs in botulism. In belladonna poisoning mild cerebral symptoms regularly occur. The face and neck are flushed either uniformly or in blotches; there is an erythematous eruption of the throat and sometimes generally over the skin resembling that in scarlet fever; the respirations are rapid and deep; the arterial pressure is above normal and the patients pass into a chattering delirium with confusion or even into a maniacal condition; there may be a rise of several degrees of fever. Concentrated urine dropped into a cat's eye will dilate the pupil. In the final stages the heart fails, the blood-pressure is low and death takes place from failure of respiration.

Curare, a South American arrow poison, produces death by respiratory paralysis, as does also conium or poison hemlock. Socrates noted while dying of this poison that there was a paralysis with slight numbness beginning in the toes and gradually ascending until it involved the trunk. Gelsemium acts peripherally like conium, but is more depressing centrally. It has an atropine-like action on the pupil and accommodation.

Veronal Poisoning. I have seen two patients undoubtedly suffering from veronal poisoning, one of which resembled encephalitis. She showed after the ingesting of 105 grains of veronal over a course of four days marked double ptosis, double vision, pronounced lateral nystagmus (except when the eyes were at rest), negative pupils, normal reaction to light and distance, no paralysis of cranial or other nerves, no retinal changes, no gastrointestinal disturbance, no diminution of secretion.

Methanol or Wood Alcohol Poisoning. Since the advent of prohibition there has arisen a formidable mass of literature upon this subject. In acute methanol poisoning there occurs: (1) Unconsciousness terminating either in death or recovery of mentality before twenty-four to forty-eight hours; (2) cyanosis; (3) pupils equal and enlarged, sometimes widely dilated with sluggish reaction to light; (4) respirations slower than normal, ten to twenty per minute; temperature, 98.6° to 100° F. Chemical analysis of early catheterized urine may show presence of formaldehyde; the stomach content may contain methanol. The most striking evidence of this poisoning is blindness, due to optic neuritis fol-

lowed by atrophy, which has been known to occur after the ingestion of so small a quantity as a teaspoonful or two.

Acute methanol poisoning may present: (1) A mild intoxication with some dizziness, nausea and mild gastrointestinal disturbance followed in a few days by recovery, but occasionally resulting in more or less serious damage to vision; (2) more pronounced effect with marked dizziness, outstanding persistent nausea, more or less severe gastroenteritis, dimness of vision frequently increasing to blindness; (3) overwhelming prostration with coma and death. The patient invariably dies in an unconscious condition, or having regained consciousness suffers relapse and death follows shortly. Generally will be witnessed in severe methanol poisoning what appears to be the ordinary effects of alcoholism—vertigo, nausea, cloudiness of mental functions, exaltation of ideas, general malaise, muscular incoördination and disturbance of vision; blindness may take place very suddenly. The condition of the optic nerve and the mental condition should clearly differentiate it from botulism and poliomyelitis.

Poison from decomposed fish and shell fish bears resemblance to botulism, but the symptoms of poisoning follow more quickly after ingestion of food, is marked by predominating gastrointestinal disturbances and the well-known skin manifestations, specially urticaria.

Conclusive proof of the diagnosis of botulism rests in the recognition of the presence of the toxin of bacillus botulinus or the discovery of the organism itself, which is always present in the contaminated food. The suspicious food and the containers of it should be carefully searched for and subjected to bacteriologic tests such as described by Meyer. Inasmuch as the toxin of type A, which commonly gives trouble in the United States, is poisonous to chickens, Graham has suggested the feeding of suspected material to chickens, which will show characteristic manifestations of botulism. It should be remembered that the ingested food may remain for many days in the stomach and in the intestines of the patient. This fact should be taken advantage of in examining the intestinal content of the patient as well as the stomach content for bacillus botulinus and for its toxin.

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THE STATUS OF EXERCISE IN THE TUBERCULOUS CONSIDERED FROM A NEURO-MUSCULAR VIEWPOINT.

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It is the purpose of this paper to record the more important mechanistic changes incident with physiologic exercise, and at the same time to parallel the maladjustments as they occur in the individual who is suffering from an active tuberculosis.

Muscular exercise should be considered from the standpoint of a neuro-muscular system, and we should ever bear in mind the continual adjustments which are occurring in the respiratory and circulatory mechanism. Exercise produces a subconscious concentration of energies of the higher nerve centers, and it is this expenditure which we must conserve. Furthermore, an improper conception of its character will be attained if it is considered as a purely muscular act. For a person to enjoy muscular exercise it is necessary that the movements of the skeletal muscles and those of the respiratory and circulatory system should be coördinated and integrated into a unit, as they are indissolubly linked together.

Exercise is purely an outward expression of neurogenic action, and when once it is initiated, the different processes then occur in sequential order until the action resembles a machine; and considered from this viewpoint it is not difficult to understand that inefficiency of any part of the mechanism would inevitably spell defeat.

A man's nervous organization is as important as his muscular development, and his ability for performing muscular work is not altogether gauged by the size of the musculature. As a rule the heart is the limiting factor which gauges exercise. Every voluntary movement adds to the work of the heart: (*a*) by increasing the output because the larger venous inflow; (*b*) the blood is expelled against a higher arterial pressure.

The source of muscular energy is to a large extent derived from carbohydrates and fats, and the belief that protein furnishes a portion of energy has long been abandoned. The conversion of potential into kinetic energy involves the liberation of lactic acid, which is an intermediary product of carbohydrate combustion. During the process of muscular exercise lactic acid is oxidized within the muscle, if the exercise is not too violent; in event that it is strenuous it then escapes into the blood stream.

It might be well at this point to introduce the method we employ in all cases of active disease. Every case is immediately placed in bed, the period of rest is variable, and not infrequently we find it necessary to confine cases to the prone position from eighteen

months to two years. All trays are served in bed, and the only exercise permissible is toilet exercise. If there is one single factor which has enhanced the results in the last few years it has been the proper appreciation of rest. It is our plan to carry rest to the n'th power, and I am of the opinion that our results would be somewhat hastened if we insisted that the patient maintains the prone posture and not be allowed the laxity of sitting up in bed for long intervals.

From the foregoing remarks the influence of attitude may seem superfluous to the reader, but even a change of position from lying down to sitting or standing has a definite effect on both the consumption of oxygen and the pulse-rate. There is an approximate increase in the pulse-rate of 25 per cent and an increase in oxygen consumption of 20 per cent. This can be explained on the assumption that a greater number of impulses are coursing from the cerebral cortex to the bulb, or, in other words, utilizing the same mechanism brought into action as that occurring at the outset of exercise. Furthermore, very little energy is necessary when lying down, but if allowed to walk it requires 100 per cent more expenditure.

At the outset of exercise impulses pass from the higher centers, and probably mainly from the motor area of the cerebral cortex to the medulla. The irradiation of impulses which occur stimulates the vasomotor, respiratory and cardio-inhibitory center, raising blood-pressure and increasing pulse-rate and respiration. Simultaneous with this impulses are sent to the skeletal musculature via the pyramidal tracts and down the cord through the lateral splanchnic motor-cell columns to the V–XII thoracic segments, producing a constriction of the splanchnic area. With a contraction of the skeletal muscles and a forcing of the blood from the splanchnic area there is an increased venous pressure, and also the diastolic volume of the heart is greatly increased. When once exercise is thoroughly instituted the muscles squeeze the blood from the smaller capillaries into the larger veins and in this manner act as a subsidiary pump.

Coincident with muscular contraction lactic and carbonic acids are formed, also acid metabolites. It seems that in almost every type of exercise the oxygen supply is inadequate for complete oxidation, and particularly lactic acid makes its entrance into the blood stream, which immediately affects the hydrogen-ion concentration of the blood. There is an equilibrating force which now comes into action and the "buffer substances" or alkali reserve of the blood attempts to equalize the condition—that is, the lactic acid reacts with the plasma bicarbonate forming carbonic acid. Carbonic acid in solution acts as an acid, and this produces an increased pulmonary ventilation by its action upon the respiratory center. By increasing the pulmonary ventilation additional work is thrown upon the heart, as the output of the heart is directly proportional to the consumption of oxygen.

It is our observation in tuberculosis that a high-grade toxemia may exist without the presence of temperature. Toxemia in itself changes the chemical composition of the blood by raising hydrogen-ions, and this favors necrosis of tissue. Exercise in the individual actively tuberculous plus a moderate grade of toxemia can attain but one end, and that is tissue-destruction.

I am of the opinion that healing is greatly facilitated when the hydrogen-ion concentration of the blood remains as nearly as possible at a normal level. It is a notorious fact that a portion of the healing which occurs in tuberculosis is due to the deposition of lime salts; especially is this true if there have been areas of caseation. If some condition, such as exercise, is superimposed upon this preëxisting condition, then the reaction of the tissues swing toward the acid side, with a depletion of "buffer substances" in the blood. Hence the healing is delayed, as it is dependent in a measure upon the alkaline salts.

Bradley and Taylor[1] have put forward the view that the hydrogen-ion concentration within the tissues is an important factor in the building up or breaking down of tissues, as the case may be. They have adduced evidence that when the reaction of the blood swings toward the acid side reserve protein is transformed into "available protein," and this undergoes autolysis. They are of the opinion that a greater blood supply and a more complete removal of acid products may reverse the process and lead to a laying down of reserve protein and, therefore, to growth of the cell. This view is very suggestive that the tissues are quite susceptible to the medium in which their activities are carried on. It is quite plausible that a shifting in the point of equilibrium would bring about autolysis on the one hand and a synthesis of tissue on the other.

In the early phase of exercise the higher centers are utilized to great advantage, but later these changes are produced by chemical means. The hydrogen-ion not only acts upon the respiratory center but it also lessens the tone of the arterioles and capillaries and maintains an adequate supply of oxygen to the part. Furthermore, it accelerates the dissociation of oxyhemoglobin to the muscles and acts upon the vasomotor center.

Maladjustments of the cardio-respiratory mechanism produce interesting symptoms. Practically every symptom which occurs is explainable either upon a mechanic or neurogenic basis. One of the dominant features evidenced by ill-advised exercise is the rapidity of the heart, and frequently the patient becomes extremely cautious because of the palpitation. It is fair to assume in any chronic disease in which there is wasting of musculature that the nutritive condition of the heart must also suffer. In many cases of tuberculosis the heart has undergone a physiologic atrophy, due to

[1] Studies on Autolysis, III. The Effect of Reaction on Liver Autolysis, Jour. Biol. Chem., **25**, 261.

a lessened venous inflow. Primarily this is caused by costal inspiration, which lowers arterial pressure. As a sequel to the above we would expect a loss of contractile power of the heart, and such does occur, due to ventricular thinning. When exercise is instituted in these individuals the mechanical pumping action of the peripheral muscles squeeze the blood from the smaller vessels into the great veins, raising venous pressure and increasing the diastolic volume of the heart. The heart now dilates to its physiologic limits, but with some loss of contractile power it is unable to empty itself at the end of systole. To maintain the minute volume it is necessary that compensation occur, and this is effected by an acceleration of the pulse-rate or palpitation.

The early coördinating mechanism of exercise sends impulses via the descending tracts in the cord to the stellate ganglion, thus activating cardiac musculature and also to the vagal center producing a lessened tone. There are many cases, especially the incipient type, in which the palpitation is purely neurogenic. Furthermore, it is well to bear in mind the effects of costal inspiration and its relation to arterial pressure. It is not an uncommon occurrence in our cases for the pressure to drop below 100 mm. Hg and frequently below 90 mm. Markwalder and Starling[2] have shown that the coronary circulation is dependent upon the tone of the coronary vessels, but to a greater extent upon arterial pressure, and in the event that the pressure falls below 90 mm. Hg the blood supply is inadequate for the nutrition of the heart. The type of case which is most liable to show this is one in which fibrosis is extensive, and there is an associated pleuritis from apices to base. The heart being unable to adjust itself to this environment will attempt compensation and dilatation follows, which is the closing act in practically all forms of pulmonary tuberculosis.

Rise in body temperature during exercise is dependent upon the severity of the exercise. It is not uncommon to record a physiologic rise of 102°F. Loss of heat is dependent upon the outside temperature, humidity, presence or absence of winds and the nature of clothing worn. Dissipation is hastened in the patient who is lean and sparse, but a great deal slower in one possessing a large amount of subcutaneous tissue. Rise in the temperature of the body heightens the excitability of the nervous system and hastens metabolism. Physiologic rise involves carbohydrate and fat oxidation while a pathologic elevation produces protein destruction. Recent metabolic findings have shown that protein oxidation is not as great as we were formerly taught.

As impulses leave the cerebral cortex there is a wide distribution both supra- and infrasegmentally, and while a great many spend their momentum upon volitional control, an equal number activate

[2] A Note on Some Factors Which Determine the Blood Flow Through the Coronary Circulation, Jour. Physiol., **47**, 275.

those structures supplied by the vegetative system. During this dissemination stimuli are sent to the central sympathetic apparatus (Edinger) located in the midbrain and then migrate down the lateral splanchnic column, stimulating motor cells of sympathetic division and thereby producing a peripheral vasoconstriction and lessened dissipation of heat. Any impulse reaching the tuber cinereum, corpus striatum or any of the subsidiary thermogenic centers would produce a like result.

Those endocrine structures receiving a similar nerve supply become activated to a greater extent, and this probably accounts for the increased metabolism. Furthermore, the destruction of any foreign protein paraenterally shows a predilection for this particular division of the nervous system. Temperature should be considered as a beneficial phenomenon, and is simply the war that is being waged between the tubercle bacilli and the specific proteolytic enzymes generated by the tissues, and only by this procedure can organisms be annihilated. No longer should it be considered as a distinct entity, and we should bear in mind the numerous extraneous factors which may either cause elevation or depression, and remembering that toxemia is only one cause which provokes pyrexia. There are a great number of individuals who are distinctly sympathicotonic, and temperature in their respective cases is of least import.

When the activity within the lung has become quiescent the patient is then allowed to sit up, beginning with ten minutes each day and increasing ten minutes until they are sitting up either three or four hours. Exercise is then instituted, and the type most frequently resorted to is walking. Why should walking be given the preference over other forms of exercise? We unconsciously attempt to prescribe some form of exercise which is the most economic from the viewpoint of nerve expenditure. Every individual is trained in walking, and by utilizing this fact they receive the optimal benefit, and at the same time we are conserving the nervous system. Useless and ineffective movements are eliminated when we prescribe an exercise with which the patient is accustomed.

Every case should be individualized relative to exercise and never force walking to the point of fatigue. In the event that the patients complain of tiring no additional exercise should be indulged in until they are able to carry out their prescribed distance with comfort. The causation of the sensation of fatigue is rather obscure. Mosso long ago stated that "nervous fatigue is the preponderating phenomenon and muscular farigue also is at the bottom an exhaustion of the nervous system." There appear, however, to be two types of fatigue: one arising entirely within the central nervous system and the other in which fatigue of the muscles is superadded to that of the nervous system.

It has been suggested that fatigue may be produced by exhaustion

of the store of energy within the muscle and the clogging of the muscular machine by the metabolic products. During exercise the steady outflow of impulses to the muscles, the complex neural processes involved in any voluntary movement and the focussing of the attention upon the exercise must involve considerable expenditure. Hence it is easy to see that fatigue could be induced with very little exercise unless the walking is carefully gauged.

I have attempted to visualize exercise from a different phase than it is usually attacked and to appreciate the significance of the various symptom-complexes which may be produced in consequence of a pathologic process affecting the lungs.

POSTOPERATIVE MASSIVE COLLAPSE OF THE LUNGS.

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Rather singularly the subject of massive collapse of the lungs as a postoperative complication has scarcely been mentioned in American medical literature up to the present time, and only by English or Canadian authors. The importance of its consideration is accentuated by the fact that it undoubtedly occurs very commonly both in civil and military practice, and also because it is frequently confused with other more or less common postoperative pulmonary complications such as pneumonia, pleuritis, pleural effusions, etc.

Attention was first drawn to the occurrence of massive collapse of the lungs by W. Pasteur,[1] who cited 34 cases as occurring with postdiphtheritic paralysis of the diaphragm or other accessory respiratory muscles in 1890. It is interesting to note that Pearson-Irvine, in 1876, made the observation on cases which undoubtedly were cases of massive collapse, "That the physical changes observed in the lungs were the result of paralysis of the muscles concerned in the elevation and expansion of those parts." In a later series of 64 cases of postdiphtheritic phrenic paralysis, with 15 fatal results and with autopsies on 8 of these, Pasteur was able to demonstrate the gross pathology in 5, the others proving to be cases of bronchopneumonia. The cases were all bilateral, in a more or less advanced collapse, and all presenting the same characteristics *en grosse*, the parts being entirely devoid of air, of a deep, definitely circumscribed blue color and sinking entirely in water. Pasteur noticed the similarity in the symptomatology between numerous clinical cases developing postoperatively and these cases of postdiphtheritic paralysis

[1] Internat. Jour. Med. Sc., 1890.

with collapse of the lungs. In 1908, in the Bradshaw lecture before the Royal College of Physicians, he drew attention to the condition, since which time he has encountered an increasing number of these cases and a corresponding diminution in those of postoperative pneumonia.[2] The clinical features were accurately described, the diagnosis elaborated, and in 1914[2] he published an article drawing attention to its frequency. Of 201 lung complications out of 3559 cases, in the Middlesex Hospital between 1906 and 1910, he found 12 cases of massive collapse, with 1 death; in frequency less than pneumonia, bronchitis or dry pleurisy, but more common than embolism, abscess or pleural effusion. It was found to occur with all methods of anesthesia, and occurred following operations on all areas of the abdomen.

About the same time Pasteur wrote his contribution in 1914, Dingley and Elliott[3] published an article in the *Lancet*, inspired by Sir Rickman Godlee, who showed them several cases encountered in his practice. During a period of two years the writers observed 11 cases, all of which followed abdominal operations. Their contributions to the literature is noteworthy chiefly on account of their consideration of the possible causes of this condition. They recalled Lichtheim's[4] observations, made in 1878, in which he had produced a condition similar, in rabbits by introducing laminaria plugs into the bronchi, resulting in a collapse of the lung tributary to the bronchus, which was the subject of the experiment. The alveoli were passively closed by absorption of the air content into the circulating blood, producing thereby a negative pressure, causing the neighboring organs to be dislocated. Dingley and Eliott conclude that in man, in addition to the comparative immobility of the thoracic wall, secretion blocks the smaller bronchioles, with the result that collapse ensues, just as in Lichtheim's animal experiments. Pasteur postulated an active collapse of the lungs, with an absence of any obstruction to the air passages, which he thought was induced by reflex inhibition of the diaphragm. He believed the collapse, to put it simply, to be due to alveolar expulsion rather than alveolar absorption.

Rose Bradford[5] devotes a chapter to the consideration of this subject in a recent *System of Medicine*, in which he refers largely to previous articles written by him in 1918–1919.[6] His experience was largely with military practice, with a large incidence, particularly in gunshot wounds of the chest, in which injuries he believes it occurs in 5 to 10 per cent of the cases. He points out that in gunshot wounds of the head or arms massive collapse has not been known to occur, but is occasionally seen as a complication in wounds of the

[2] British Jour. Surg., vol. **1**.
[3] Lancet, London, May, 1914.
[4] Arch. f. exper. Path. u. Pharmakol., **10**, 54.
[5] Oxford Loose-leaf Medicine.
[6] Quart. Jour. Med., 1918–1919.

buttocks, pelvis and thighs, assuming therefrom that the degree of immobilization is a factor in its production.

Briscoe,[7] in 1920, emphasized the effect of deficient respiratory excursion and a recumbent posture in causing diaphragmatic fixation with pleuritis, and coincidently pulmonary deflation.

Recently, Scrimger[8] in his article speculates on the various theories heretofore promulgated regarding the causation of massive collapse, and adds his belief that the lesion is probably due to an abdominal interference with the vagus control, causing a contraction of the muscular elements of the lung, aided by the subsequent collection of mucus in the bronchi sufficient to prevent the egress of air and leading to absorption of the alveolar air content and ultimately collapse. His article is interesting, particularly on account of the roentgenographic studies, which in some of his cases show most extravagant alterations in the relationship between the intrathoracic organs.

It is my belief that various factors may produce the lesion and that they are probably never entirely single, except in postdiphtheritic paralyses, in which the immobility of the diaphragm is so extreme as to be strikingly conclusive as to its being the cause. One must bear in mind that on the one hand Lichtheim's experiments are difficult to refute with his careful experimental technic, whereas on the other hand the evidence offered by postdiphtheritic phrenic paralysis is equally incontrovertible. There is no doubt that the recumbent position, as emphasized by Rose Bradford and Briscoe, is an important subsidiary factor as well as deficient aëration of the lungs. It is probable that in civil practice the incidence is more common in abdominal surgery, leading to more or less fixation of the diaphragm, due to a reflex inhibition, with an effort to cause a splinting action on account of the neighboring trauma. The theory that the recumbent posture is a factor is corroborated by the non-occurrence of massive collapse in injuries not requiring immobilization of the body such as injuries to the head and arms, as observed by Rose Bradford. The admonition to take deep breathing exercises systematically after operations would not only promote aëration of the more distal parts of the bronchial tree, but would also tend to reduce the immobility of the perithoracic musculature. I think it reasonable to assume that with the lack of mobility in the accessory muscles of respiration and the diaphragm, pulmonary expansion and retraction are necessarily limited. Mucus is formed and not expelled, causing an obstacle to the ingress of air into the smaller bronchioles, leading to ultimate alveolar absorption of the air into the circulation.

Bronchial obstruction, therefore, and muscular immobility tend to bring about this condition, one factor or the other predominating,

[7] Quart. Jour. Med., 1920.
[8] Surg., Gynec. and Obst., No. 6, 32.

however, in individual cases, leading to alveolar absorption, and finally the condition of massive collapse.

The extent and the site of involvement in massive collapse vary considerably. In most cases there is only a partial involvement of one of the lower lobes of the lungs; in others the condition is more extensive, involving a whole lobe or even an entire side. It is rather frequently bilateral. The noteworthy feature is the fact that in unilateral trauma collapse occurs not only on the side affected but oftentimes on the contralateral side, as was pointed out by Rose Bradford and others.

Physical Signs and Symptoms. The physical signs and symptoms of massive collapse are so distinctive that it is curious that the condition has not been recognized more commonly and described more frequently. A careful study of the case will make differentiation from conditions simulating it very easy. The exciting factor varies a great deal, and any trauma, either accidental or otherwise, necessitating more or less immobilization of the body may bring about the condition. It has been known to follow all methods of anesthesia, has occurred with local anesthesia and without any anesthesia at all. Aside from military practice I believe that in civil life it will be found that abdominal operation is the most frequent cause of the condition, on account of its immediate effect in requiring immobilization, producing immobility of the diaphragm and deficient aëration of the lungs. The condition may develop within a few hours or as late as one week after the exciting trauma. The onset is sudden, the course either rapid or at times protracted and resolution either prompt or slow. The degree of temperature is usually very moderate, but may be as high as 103° or 104°F, the coincidence of inflammatory phenomena probably influencing the height of the temperature curve. The respiration rate is increased by the immobility of the affected part, by an accompanying pleuritis or by toxic conditions incident to inflammatory complications. The pulse-rate is found to be more or less in direct relationship with the respiratory and thermic changes, but is less marked in uncomplicated cases, as would be naturally inferred.

On examining the chest one is impressed by the diminished or absent excursion of the chest wall over the affected area. The cardiac impulse is displaced toward the affected side and is as marked in the left-sided cases as in those occurring on the right side, the apex having a tendency to tilt outward and upward, so that the apex-beat may be felt in the axilla. In right-sided affections the impulse may be felt at the tip of the sternum or to the right of it. These signs are corroborated by roentgenographic study, the heart retraction being most marked, the dome of the diaphragm ascending to an unusual degree and the pulmonary area appearing partially or totally collapsed. In bilateral affections the displacement of the heart is absent, but the high position of the diaphragm and the

collapse of the lungs are easily manifest. On palpation the intercostal spaces on the affected side are found to be narrowed, leading to a relative approximation of the ribs. The percussion note over the affected area is dull and may approach flatness. Rose Bradford points out that in left-sided cases the lower part of the chest wall is highly resonant, due to the abnormally high level of the diaphragm, the liver interfering with this symptom in right-sided cases. Breath sounds and fremitus are usually increased, sometimes enormously so, but may be diminished or absent. The transmission of voice sounds may be so intense as to approach whispered pectoriloquy.

Bronchophony was present in all of my cases, and in no case was there diminution of the breath sounds or fremitus. No doubt the alteration in the transmission of sounds is due to the relative proximity of the affected area to sound-conducting bronchial tubules. Rales are usually absent in the early stages, but supervene as the case progresses, probably due to a bronchitis, resolution or an occasional pneumonia developing. In a great many cases a pleural friction rub is plainly audible. In the later stages of the condition, when expectoration is rather profuse and resolution occurs, rales are more frequent. As resolution occurs the heart gradually returns to its original position, the lungs slowly expand and the diaphragmatic dome flattens out.

The extent of the symptoms and the ease of recognition depend, of course, upon the amount of lung tissue involved and as to whether the condition is unilateral or bilateral. It is readily understood also that the influence of the condition on the patient's economy is dependent largely upon complicating factors as well as upon the extent of the lesion. Dyspnea may be moderate or extreme, as it usually is in bilateral cases. The cough is slight, as a rule, in the beginning, with a rather scant expectoration, but in the later stages it is accompanied by an expectoration of profuse mucopurulent sputum. My experience bears out the previous observation that the sputum is rarely or never bloody—an important consideration in the differentiation between pneumonia or infarct and collapse.

Bronchitis, pleurisy and pneumonia are recognized as complications. Effusion has been known to follow pleurisy. A differentiation must be made between pneumonia, hypostatic congestion of the lungs, embolus, infarct, pleuritis (with or without effusion), hemothorax and massive collapse. When one bears in mind the outstanding pathognomonic signs of massive collapse, confusion with other conditions is difficult. One must bear in mind that the affected side is retracted and does not expand with inspiration. The diaphragmatic and cardiac displacement is extreme and the general symptoms invariably less severe than with pneumonia or embolus. The very marked dulness, the extreme increase in the breath sounds (as usually noted), the scant expectoration, the comparative absence of constitutional signs in the non-occurrence of

complications, accompanied by displacement of the heart and diaphragm and roentgenographic studies, easily establish the diagnosis.

The prognosis is invariably good, but bilateral cases, or cases affecting more than one lobe, are more apt to be fatal, particularly in debilitated subjects.

A brief case report of the cases occurring in our practice is submitted, chiefly because of the interesting autopsy findings in the fatal case:

CASE I.—Mrs. D., aged thirty-eight years, was admitted to St. Mary's Hospital, Duluth, November 19, 1920. Her general condition was good.

She was operated upon November 20, by Dr. W. A. Caventry, for the removal of an ovarian cyst and appendix. The gall-bladder and stomach were examined and were found normal. Her temperature before operation was 98.6°F. and the leukocyte count 9000.

November 22 (two days after the operation) the pulse rose rapidly from 90 to 130 and the temperature to 101°F. The temperature and pulse varied little from this day until November 25, when there was a gradual reduction, day by day, until normal on November 28. The leukocyte count on November 22 was 21,200 and on November 25 it was 14,600.

Physical Findings. There was limitation of motion on breathing of the left side of the chest. There was marked dulness over the lower lobe of the left lung. Bronchial breathing was present over the area of dulness and no rales were heard. The left border of the heart extended nearly to the axillary line and the apex-beat was felt in the fifth interspace, 5 cm. outside the nipple.

There was no change the following day except that the bronchial breathing was further increased.

November 25, when the patient's condition was better, the left border of the heart had approached its normal position, the bronchial breathing had become vesicular and mucous rales were heard.

CASE II.—Mr. W., aged forty-nine years, was admitted to St. Mary's Hospital, Duluth, June 23, 1921, with an acute appendicitis. The temperature was 100°F. and the leukocyte count was 20,000.

He was operated on the same day, by Dr. T. L. Chapman. A gangrenous appendix was removed and was closed without drainage.

June 24, the day following the operation, his temperature rose to 102°F. and the pulse to 110. The patient was apparently distressed. Examination of the chest showed an area of dulness, approaching flatness, corresponding to the lower right lobe. Moderate bronchial breathing with increased transmission of whispered sounds. The left border of the heart was displaced to the right about 6 cm.

The following day the patient's condition was about the same, but the temperature had risen to 104°F. and the pulse to 120. The physical signs were the same. There was still an absence of any rales. In the evening of June 25 the temperature dropped to 99°F. and the pulse to 85; the patient was apparently much better.

The following morning the right lower chest was resonant, a few rales were heard and the heart approximately was in the normal position.

CASE III.—Mr. E. J. M., aged forty-eight years, was admitted to St. Mary's Hospital, Duluth, April 2, 1921, and was operated on April 6 for a chronic duodenal ulcer. An appendectomy and posterior gastroenterostomy were done.

April 8 the patient suddenly developed acute respiratory distress, with moderate cyanosis. The temperature at that time was 99°F. and the pulse was 110.

April 9 his temperature was 101°F.; pulse, 140; respiration, 38. Physical examination showed the patient to be in severe distress, with difficulty in breathing and in an apprehensive condition. The bases of both lungs expanded poorly. The vocal and tactile fremitus were increased on both sides. Dulness was extreme. On auscultation there was marked increase in the transmitted breath and whispered voice sounds. There was no displacement of the apex-beat. The patient's condition was too grave to permit of roentgenographic studies, became rapidly worse and he died on April 10.

A partial autopsy was permitted, consent being given to open the operative wound. This was found to show moderate healing and was void of any visible evidence of infection. The site of the gastroenterostomy and the appendicular stump were clean and without adhesions. It was necessary to deliver the lungs through the diaphragm, which was done without very much difficulty. The appearance of the lower lobes on both sides was most striking. Definitely circumscribed areas involved nearly the whole of both lower lobes, sharply demarcated from the normal tissues by a deep violet color. The collapsed areas were definitely depressed in relation to normal lung tissue, and contained no air, blood nor pus in the alveolar areas. The upper lobes were normal in appearance and showed no evidence of hypostatic congestion.

Cut sections from the affected area did not float in water.

Microscopical section showed an approximation of the alveolar surface to a marked degree, with a few red and white blood cells in the alveolar spaces. The interalveolar tissue was normal.

The autopsy findings were otherwise entirely negative.

Attention is called to the relative frequency of this condition and the importance of its recognition from a diagnostic standpoint.

BACTERIAL ENDOCARDITIS AS A SEQUEL TO SYPHILITIC VALVE DEFECT.

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Ever since the advent of subacute bacterial endocarditis as a clinical entity it has been recognized that a previous valve defect was almost a *sine qua non* in the causation of the disease. The vast majority of these defects are of rheumatic origin, with a scattering few due to other infections, congenital heart disease or arteriosclerosis. As a cause of valve defects in general, rheumatic fever comes first, with syphilis probably second; yet with the very frequent occurrence of syphilitic endocarditis of the aortic valve, the combination of subacute bacterial endocarditis and syphilitic endocarditis seems to be a decided rarity. This assertion is made not only on the grounds of personal experience, but also on the basis of a scrutiny of the papers dealing with the subject over the last decade. The valve affected by syphilis is practically always the aortic. Likewise is it very true that in a considerable number of cases of bacterial endocarditis it is this valve alone that has been involved, this point being emphasized by Cotton[1] last year in a report made to the British Medical Research Council. Be this as it may, however, an analysis of the various reports shows an overwhelming predominance of rheumatic lesions and an insignificant incidence of syphilis. Libman seems to be the only author who discusses the relationship at all.

Two of Osler's[2] patients had old aortic lesions alone, one with a history of previous arthritis and one without, but neither had anything suggestive of syphilis and neither came to postmortem. In Horder's[3] elaborate series of 150 cases only 2 gave a history of previous syphilis, although out of 118 examined at necropsy 22 had aortic involvement alone. Nothing is said of the condition of the aorta in these cases, since most were studied in the pre-Wassermann era, before the relationship between syphilis, aortitis and aortic insufficiency was realized. In Billings[4] 14 cases there was only one aortic lesion, and this was definitely rheumatic.

Libman, who has made a more intensive clinical study of bacterial endocarditis than anyone else, several times speaks definitely on

[1] Subacute Infectious Endocarditis, British Med. Jour., 1920, **2**, 851.
[2] Chronic Infectious Endocarditis, Quart. Jour. Med., 1908–9, **2**, 219.
[3] Infective Endocarditis, Quart. Jour. Med., 1908–9, **2**, 289.
[4] Chronic Infectious Endocarditis, Arch. Int. Med., 1909, **4**, 409.

this question. In the course of a discussion[5] of valvular disease he says, "The number of instances of valvular defects of rheumatic origin which have become the seat of non-rheumatic or non-syphilitic endocarditis is remarkably large compared to the number of instances in which this occurs on the basis of valvular defect due to lues, considering that lues is such a close second to rheumatism in the causation of valvular disease," and in 1918, in a study of 182 personally observed cases of subacute bacterial endocarditis,[6] he practically repeats this statement. No figures are given, however, of the actual number of instances in which syphilitic valves have subsequently become bacteria-infected. At the symposium on infectious endocarditis at the 1920 meeting of the British Medical Association he again says,[7] "It is interesting to note that the subacute bacterial infections occur mainly on the basis of valvular defects due to the rheumatic virus, and much less in other types, notwithstanding the great frequency of syphilitic valvular defects." Horder[8] at the same meeting states that "any old-standing lesion is good enough to serve as the secondary focus of infection," but he, as well as nearly all those taking part in the discussion, strongly emphasizes the predisposing influence of rheumatic fever.

Cotton[9] has made some interesting studies not only of infectious endocarditis but also of aortic disease, using soldiers attending a British Army heart clinic. He found that 8 per cent of the patients with valvular disease, comprising a series of 55 cases with an average age of thirty years, had subacute bacterial endocarditis, and of these, 33 had aortic lesions alone and 14 had aortic regurgitation as well as mitral stenosis. He makes no mention of preceding syphilitic aortic lesions, however, although 7 of the 55 had a positive Wassermann reaction and 1 a history of syphilis. In his study[10] of 50 cases of aortic insufficiency with an average age of thirty-one years, he obtained a history of rheumatic fever in 27 per cent and syphilis in only 2 per cent. A Wassermann test was done in 35 of these and was positive in 8, but of these all except 1 was over forty years old. He agrees with the commonly held opinion that rheumatic fever is the most important factor in the production of aortic lesions in patients under forty years, while syphilis plays an equally important part after forty years. Although he gives no other data, and in fact does not discuss the matter, one feels that the incidence of preceding syphilitic valvulitis in his 35 cases of bacterial aortic endocarditis was slight, specially since his material was comprised mainly of young men.

[5] Libman, E.: Affections of the Valves of the Heart, Med. Clin. of North America, 1917–18, **1**, 573.

[6] Libman, E.: Streptococcic and Influenzal Endocarditis, Med. Clin. of North America, 1918–19, **2**, 117.

[7] Libman, E.: British Med. Jour., 1920, **2**, 304.

[8] British Med. Jour., 1920, **2**, 301.

[9] Loc. cit.

[10] Cotton, T. F.: Observations on Aortic Disease in Soldiers, Lancet, 1919, **2**, 470.

Just why there should be this apparant immunity of the syphilitic valve to secondary infection affords an interesting field for speculation: First, and probably most important of all; the age incidence of the two diseases plays a very considerable part. Syphilitic endocarditis is found most frequently after thirty-five, while bacterial endocarditis occurs under that age in a large majority of the cases. As rheumatic fever is the greatest offender in the production of valve injuries, and is at the same time preëminently a disease of youth and young adult life, it is only natural that it should be the commonest precursor of an infection which selects a damaged valve in a young person as its objective. (2) There is possibly something to be said from the bacteriologic standpoint. The overwhelming majority of the cases of bacterial endocarditis have shown a non-hemolytic streptococcus to be the infective agent. It is by no means improbable that some of these cases owed their early valvular disability to the same organism in an attenuated form, the disease running a milder course with slight valve damage and no septicemic characters, but with streptococci lying dormant in the valve lesions and later lighting up into the terminal infection. This again would cut down the proportionate incidence of syphilis. (3) The anatomic changes occurring in the valves themselves may be a factor. Valve damage means increased vascularity, which has been held to be a predisposing influence in subsequent bacterial infection.* This view has been strengthened by Bayne-Jones's[11] demonstration of the valve capillaries, thus affording an anatomic basis for the earlier theories of Köster and Rosenow of the embolic origin of endocarditis. The more vascular is a valve the more readily is it open to later bacterial invasion, and the essential differences between the mode of formation of a verrucose endocarditis and a syphilitic endocarditis speak for a greater vascularization of the former after partial healing has occurred.

The following case is an example of a subacute streptococcus endocarditis which occurred in a patient suffering from syphilitic aortitis and aortic endocarditis, terminating in death and going to necropsy. Only the essential points in the history, examinations and pathologist's report have been set down.

On July 7, 1920, a steamfitter, aged thirty-five years, came to the outpatient department of the University of California Hospital with the complaint of "stomach trouble." His family history was of no bearing. There had been a chancre at fifteen years but no secondary manifestations. He had had five Neisser infections, the last four years before. The left leg had been broken as a boy. He had had a varicose vein operation on the right leg in 1907 and again in 1917. In 1918, the army had rejected him on

[11] Bayne-Jones, S.: The Bloodvessels of the Heart Valves, Am. Jour. Anat., 1917, **21**, 449.

account of a "leaking heart valve," the first knowledge he had of any heart difficulty.

In 1917, he began to have pain in the precordial region, radiating down the left upper arm, coming on specially with exertion. This would be followed by some faintness and indefinite feelings of discomfort in the epigastrium. The digestive difficulties continued and brought him to the clinic. After a heavy meal he would be troubled with a sense of oppression in the chest, pain in the upper abdomen, precordium and down the inner side of the left arm to the elbow. The attacks would come on suddenly and last two or three minutes. In the latter part of 1918 he was forced to stop work on account of the pain, although he had had no dyspnea or edema.

On examination it was found that he had lost about forty pounds, although he still looked fairly robust. The pupils were normal. The heart and peripheral vessels showed the characteristic signs of well-marked aortic insufficiency: enlargement to the left, widened arch, at the base a to-and-fro murmur, with the diastolic element very loud and a loud systolic murmur at the apex. All peripheral arteries pulsated vigorously; there was a typical Corrigan pulse, capillary pulsation, pistol-shot sound over the femorals and a blood-pressure of 120/40. The rate was 62 and regular. The abdomen showed nothing. There was a scar on the penis and the blood Wassermann was triple positive. He was given five small doses of salvarsan and some mercury salicylate injections, eventually drifting away from the clinic during the latter part of September, somewhat improved.

Nothing more was heard of him until August 1, 1921, when he entered the University of California service of the San Francisco Hospital. After leaving the clinic conditions apparently had been stationary until May, when he began to lose weight and noticed on the pads of his fingers occasional red painful spots which would last a day or so and then disappear. Since the middle of June he had been growing weaker, with night-sweats and dyspnea. There had been a loss of sixty pounds, and although he had gone to various hot springs in the hope of relief, he had failed progressively.

On examination he was quite sick-looking and presented a great contrast to his appearance of a year before. The heart was about the same but the peripheral pulsations were less marked. A few petechiæ were present over the neck and shoulders and there were rare retinal hemorrhages. There was no clubbing of the fingers. For the next two months he ran a septic type of fever, varying from normal to 102°. Petechiæ were constantly present over the neck and shoulders and a number of painful evanescent erythematous nodules appeared on the pads of the fingers. The spleen was not felt until September 1, when a soft enlargement

was noted, persisting until death. The systolic murmur at the apex disappeared permanently about this time. Anemia was progressive, going from 80 per cent hemoglobin and 5,000,000 reds at entrance to 35 per cent hemoglobin and 2,500,000 reds at the lowest point. There was a slight leukocytosis with a relative increase in the neutrophiles. The blood Wassermann was still triple positive. On account of considerable mental confusion at entrance a lumbar puncture was done, which showed a cell count of 32 normal globulins, negative Wassermann and a luetic colloidal gold curve. Microscopic hematuria was constant over a number of urine examinations. Three blood cultures were taken during August, each resulting in the isolation of a long-chained non-hemolytic streptococcus which did not form pigment on blood agar and which was agglutinated by the patient's serum in dilutions up to 1/800.

His course was steadily downward and he became very thin and weak. Toward the last there was marked cardiac dilatation, small amounts of fluid in both pleural cavities and passive congestion at both lung bases. He died October 5, 1921.

Necropsy was done by Dr. G. Y. Rusk and portions of his report germane to the subject are quoted.

Anatomic Diagnosis. Acute verrucose endocarditis, involving all the cusps of the aortic valve, with perforation of the right posterior aortic cusp and with extension of the process to the anterior cusp of the mitral valve, with small aneurysmal herniation of the same. Syphilitic aortitis with dilatation of the first part of the aorta and involvement of the ring of the aortic valve with insufficiency. Marked atheromatous degeneration with calcification of the first part of the aortic arch. Myocardial fibrosis. Subacute degeneration of subendocardium of the left ventricle. Diffuse cardiac hypertrophy. Cardiac dilatation, involving particularly the left ventricle, less markedly the left auricle and the right ventricle. Relative dilatation of the aortic and mitral orifices. Hydroperitoneum, hydropericardium and bilateral hydrothorax. Diffuse subperitoneal edema. Chronic passive congestion of the lungs. Pulmonary edema. Compensatory pulmonary compression atelectasis. Slight diffuse bronchitis. Recent infarcts in the spleen. Old scars in the spleen. Old infarct in each kidney. Acute diffuse nephritis. Secondary anemia. Thromboses in periprostatic plexus. Undescended and atrophied left testis. Emaciation.

Heart. Greatly enlarged, 550 gms. Epicardium devoid of fat, edematous in appearance, presents on the anterior surface of the left ventricle toward the apex two small, irregular, slightly depressed, scar-like areas about 3 mm. in diameter. Myocardium pale brown, rather flabby and shows definite patches of fibrosis in the left ventricular wall near the apex. Left ventricular wall measures 1 to 1.25 cm.; right, 3 to 5 mm. in thickness. Endo-

cardium pale; that of the left ventricle presents a fine diffuse mottling resembling fat deposits; section in this region into underlying subendocardial tissues shows these apparently involved in a degenerative process to a depth varying from 1 to 2 mm., and here the tissue in question appears grayish yellow, opaque and softer than normal.

Valves. Adherent to all of the cusps of the aortic valve are relatively large, yellowish-brown, verrucose masses, the largest measuring 1.5 cm. x 1 cm. x 0.75 cm. These are attached to the ventricular surfaces of the cusps, favoring particularly their line of closure, and are composed of a friable, soft, granular material. In the right posterior cusp, involving the end next to the left posterior cusp, is a large opening which apparently represents an ulcerative perforation. The cusps themselves are not unusually thickened or deformed. There is, however, a distinct spacing at their angles so that the cusps are separated from each other by an average distance of 2 or 3 mm. From the anterior cusp the vegetations proceed as a direct, though somewhat interrupted, line down on to the ventricular surface of the anterior cusp of the mitral valve. The corresponding area on the auricular surface of this cusp presents a round elevation, 0.75 cm. in diameter, which on further examination is seen to be a small aneurysmal herniation, the result of a weakening of the wall of the cusp due to the vegetations. Attached to the free border of the same cusp is noted a group of chordæ tendineæ which apparently have ruptured and whose ends are covered with vegetations. The cusps of the mitral valve otherwise appear negative. Measurements: Tricuspid, 12 cm.; pulmonary, 7 cm.; mitral, 12 cm.; aortic, 8 cm.

Heart Cavities. The left ventricle is greatly dilated, resulting in a marked blunting of the heart apex and a flattening of the papillary muscles. The left ventricular cavity extends downward 3.5 cm. beyond the apex of the right ventricle. The latter cavity likewise presents some dilatation, particularly in the region of the conus. The left auricle is somewhat dilated.

Coronary Arteries. The beginning of the right coronary is narrow, but except for this both coronary vessels appear normal. In proportion, however, to the size of the heart the caliber of the descending branch of the left coronary is relatively small.

Aorta. The arch is dilated and measures 8 cm. in circumference. The first portion of the arch shows a marked striation of the intima as well as numerous atheromatous patches, many associated with large, thin, calcareous plaques. These changes appear limited to the first 4 cm. of the aorta, which is definitely increased in thickness, averaging 4 mm. as compared with 1 mm., the thickness of the rest of the aortic arch. The remainder of the aorta, including the thoracic and abdominal portions, is in excellent condition, showing only a few scattered patches of atheroma.

Summary. From a study of the literature it would seem that the sequence of bacterial endocarditis on a syphilitic endocarditis is a decided rarity, despite the frequency of the latter condition and the fact that the former infection often has a selective action on the aortic valve. No reason can be assigned for this, although the age incidence of the two diseases probably plays some part. Another factor may be the increased vascularity of the valve previously damaged by rheumatic fever as compared with that damaged by syphilis. A case is reported of an individual suffering from a typical syphilitic aortitis and aortic endocarditis. One year later the patient enters the hospital with a non-hemolytic streptococcic endocarditis, which pursues the usual course and terminates in death. At necropsy a characteristic syphilitic aortitis with involvement of the aortic ring is found, together with an acute verrucose endocarditis of all the aortic cusps and perforation of one, with an extension into one mitral leaflet.

REVIEWS.

A Manual of Clinical Laboratory Methods. By Clyde Lottridge Cummer, PhB., M.D., Associate Professor of Clinical Pathology, School of Medicine, Western Reserve University; Associate Clinical Pathologist, Lakeside Hospital; Director of Medicine and Visiting Physician, St. John's Hospital; Director of Laboratories, St. Alexis Hospital, Cleveland, Ohio. Pp. 484; 136 engravings and 8 plates. Philadelphia: Lea & Febiger, 1922.

The author opens his treatise with a very detailed chapter on the study of the blood. This chapter includes microscopic, serologic and chemical examination methods given in full. All the modern chemical methods for blood are introduced in very clear and definite form; the concise and systematic grouping of the steps in making a chemical examination of the blood render the book of great value to the student. Examination of the urine is briefly surveyed; an excellent chapter on tests for renal function is included. Gastric contents, feces, sputum and spinal fluid examinations are each given a brief chapter and bacteriological methods as a whole are touched upon. There is a very useful appendix which covers formulas for the most commonly used stains, a list of apparatus to be assembled for routine clinical laboratory work, a useful table for equivalents of the metric and common system and one for conversion of Centigrade to Fahrenheit degrees. The book is written clearly and concisely and will be of much value to the laboratory worker, even if for the chapters on blood alone. An extensive bibliography is given, bringing the subject-matter up to date and the book is well indexed. E. Q.

Papers from the Mayo Foundation for Medical Education and Research and the Graduate School of Medicine of the University of Minnesota, Covering the Period of 1915-1920. Pp. 695; 203 illustrations. Philadelphia and London: W. B. Saunders Company, 1921.

This book is a collection of papers by students and teachers in the Mayo Foundation and Medical School, and is not to be con-

fused with the *Collected Papers of the Mayo Clinic*. Nearly all of the papers were originally in the form of theses presented by graduate medical students in partial fulfilment of the requirements for the degree of Master of Science or Doctor of Philosophy and are the result of research work. Abstracts by the authors take the place of many of the original articles, some of which have been previously published in the current literature. The list of contributors contains sixty-four names, and the diversity of subjects treated may be gathered from a glance at the titles of some of the eleven papers grouped under the heading of Alimentary Tract. These include: "The Morphology of the Digestive and Respiratory Tracts in a 20 mm. Pig Embryo;" "Some Clinical and Experimental Observations on Gastric Acidity;" "Use of the Gas-chain Method;" "A Study of the Arteries Supplying the Stomach and Duodenum and their Relation to Ulcer;" "Multiple Polyposis of the Intestinal Tract;" "Clinical Studies in Abdominal Disorders." In publishing a work of this kind the medical school advances both its own and its students' interests, while giving to the profession the results of studies which would otherwise be known only to a few. It is surprising, therefore, that more publications of this nature have not appeared from our medical schools. J. H. A.

THE SURGICAL AND MECHANICAL TREATMENT OF PERIPHERAL NERVES. By BYRON STOOKEY, Associate in Neurology, Columbia University; Assistant Surgeon, New York Neurological Institute; Assistant Professor of Neuro-Surgery, New York Post-graduate Medical School and Hospital. With a Chapter on Nerve Degeneration and Regeneration, By G. CARL HUBER, M.D., Professor of Anatomy, University of Michigan. Pp. 475; 217 illustrations, (8 in color and 20 charts). Philadelphia and London: W. B. Saunders Company, 1922.

The recent war may have served to overemphasize the frequency of peripheral nerve lesions, but their importance is manifest. There is no field of surgery in which there has been such a lamentable lack of intelligent understanding of the very nature of these lesions on the part of all but a very few specially trained in this field. In the title of this book the author gives evidence of an appreciation of the fundamental necessities of handling lesions of the peripheral nerves. Corrective surgery must be done, but it will fail unless combined with the proper mechanical treatment. The author is entirely right: Peripheral nerves should be looked upon as extensions of the central nervous system and should be handled by surgeons trained in the anatomy, physiology, pathology and surgery of the central nervous system. Nerve tissue is the most

highly specialized tissue in the body and is the least tolerant of trauma. It cannot be handled therefore in the same way that one would handle tendons.

Each subject, such as the anatomy, methods of nerve repair, direct nerve implantation and direct muscular implantation, tubulization, etc. are carefully and thoroughly considered. The chapter on Nerve Degeneration and Regeneration by Dr. G. Carl Huber is a distinct addition to the book. No one more than Dr. Huber has an authoritative right to speak on this subject. If one is inclined to be hypercritical, it might be said that some will feel the principal object in describing an operative procedure is to give a dispassionate description of its technic rather than either to omit its description because the author does not approve of it or to overemphasize some other technic which does meet with the author's approval. The reviewer finds himself, however, so in accord with the author in stating his preference for certain operative procedures that this objective is not a serious one. The illustrations are excellent and altogether the reviewer can heartily commend this book to one interested in peripheral nerves. The reviewer has found much to praise and almost nothing to criticise in this book.

J. S. R.

INTRODUCTION TO DERMATOLOGY. By NORMAN WALKER, LL.D., M.D., F.R.C.P., Physician for Diseases of the Skin, The Royal Infirmary, Edinburgh. Seventh edition. Pp. 366; 80 illustrations. New York: William Wood & Company, 1922.

THIS is one of the standard text-books on diseases of the skin, somewhat smaller in size than the average dermatological text-book. The fact that seven editions have appeared indicates very clearly that the book may be recognized as one of the acceptable text-books on the subject. The new edition contains several new plates as well as a considerable amount of new material.

J. H. M., JR.

NEOPLASTIC DISEASES. A TREATISE ON TUMORS. By JAMES EWING, M.D., Sc.D., Professor of Pathology at Cornell University Medical College, New York City. Second edition. Pp. 1054; 514 illustrations. Philadelphia and London: W. B. Saunders Company, 1922.

To those especially concerned with the study of tumors, this book has now become well-nigh indispensable. Amid the fog of medical text-books, so many of which appear to be written primarily in response to the energetic publisher's demand, and only secondarily

because the author had something valuable to contribute, Ewing's *Neoplastic Diseases* stands out like a beacon. A review of the first edition, written from the practitioner's standpoint, was printed in this journal in 1919. Let it suffice to say that the pathologist's commendation must be even greater. The second edition has added thirty-three more of the excellent photomicrographs and considerable new data to the chapters on fibroma, sarcoma of bone and bone marrow and endothelioma.

E. B. K.

AIDS TO MEDICINE. By BERNARD HUDSON, M.D. (CAMB.), M.R.C.P. (Lond.), Swiss Federal Diploma, Physician-in-charge of the English Sanatorium at Montana, Switzerland. Third edition. Pp. 370; 11 illustrations. New York: William Wood & Company, 1921.

THIS small handbook is prepared for the purpose of supplying the student with a book on medicine of a size convenient to carry around in order to refresh his memory from time to time. It apparently fulfils these requirements.

J. H. M., JR.

MODERN METHODS OF TREATING FRACTURES. By E. W. H. GROVES, Surgeon to Bristol General Hospital, Consulting Surgeon to the Lessham Hospital. Second edition. Pp. 435; 296 illustrations. New York: William Wood & Company, 1922.

FIVE years after the first edition appears this, the second edition, in which the book has largely been rewritten. The majority of the illustrations are new and the entire subject of the treatment of fractures has been brought up to date in every sense of the word. The entire subject of bone grafting is considered afresh—presenting the subject experimentally and clinically. An attempt has been made to present all good modern methods, so that the book is one for ready reference.

The author's views are sane, sound and mechanically correct. His one statement, that fractured bones must be treated by neutralizing the muscle pull in all cases, shows that he knows the principles thoroughly. When he further adds: "Until fractures receive the same special consideration accorded other surgical conditions and cease to be regarded as mere encumbrances of general surgical wards, no great progress can be made"—he shows that he has the actual and practical welfare of the broken bone at heart. He shows that the treatment of a fracture is merely begun at the time of the so-called reduction.

E. L. E.

DISEASES OF THE EYE. By GEORGE E. DE SCHWEINITZ, M.D., LL.D., Professor of Ophthalmology in the University of Pennsylvania; Ophthalmic Surgeon to the University Hospital; Consulting Ophthalmic Surgeon to the Philadelphia General Hospital and the Orthopedic Hospital and Infirmary for Nervous Diseases; Colonel, M.R.C., U. S. Army. Ninth edition. Pp. 832; 415 illustrations. Philadelphia: W. B. Saunders Company, 1921.

THE ninth edition of Dr. de Schweinitz's book on ophthalmology has been entirely revised, reset and reprinted. It is, therefore, virtually a new book with the added advantage that the author has had the benefit of the experience acquired in the preparation of the other volumes. A critical review of this work hardly seems necessary. It has been universally recognized in every English-speaking country as a standard text-book on the subject and has been accepted for many years as an ideal book on diseases of the eye.

J. H. M., JR.

SURGICAL CLINICS OF NORTH AMERICA. PHILADELPHIA NUMBER. Vol. II. Pp. 331; 145 illustrations. Philadelphia: W. B. Saunders Company, 1922.

THIS, the Philadelphia number, is contributed to by some of the best-known surgeons in the city, if not in the country. Most of the material is presented in a clear, concise and interesting manner. The greater portion of the work deals with important daily questions and it is interesting and instructive to be able to follow the reasoning of the man at the helm.

Just one or two of the articles make the book worth much to the reader, though this value were not enhanced by a dozen others.

The one criticism, if it could be so-called, is that space is given to much of unimportance in the minor details, which however from a teaching standpoint may be rightly considered commendable.

E. L. E.

THE PATHOLOGICAL GALL-BLADDER ROENTGENOGRAPHICALLY CONSIDERED. By ARIAL W. GEORGE, M.D., AND RALPH D. LEONARD, M.D. One hundred and thirty-five roentgen-ray studies on forty-five full-page plates, of which three are actual photographs, and two text illustrations.

THE first part of this work, Volume II of the *Annals of Roentgenology*, is a monograph on the radiographic study of the pathological gall-bladder. In it are discussed technic, interpretation, with all the factors entering into it, and the operative findings in

128 cases. The second part, or Atlas section, is a handsomely illustrated record of one hundred and thirty-five roentgen-ray studies showing the usual and unusual conditions encountered in the examination of the gall-bladder region. The captions of the illustrations and the introductory text of each division are printed in English, French, and Spanish. The space allotted the reviewer precludes an exhaustive criticism of this splendid volume. Suffice it to say that the authors, recognized authorities, have produced what cannot help but be a very valuable reference book.

J. D. Z.

THE PREVENTION OF MALARIA IN THE FEDERATED MALAY STATES: A RECORD OF TWENTY YEARS' PROGRESS. By MALCOLM WATSON, M.D., C.M., D.P.H., Chief Medical Officer, Estate Hospital's Association, Klang, F.M.S.; late Senior District Surgeon, F.M.S. Medical Service; with contributions by P. S. HUNTER, M.A., M.B., D.P.H., Deputy Health Officer, Singapore, and A. R. WELLINGTON, M.R.C.S., L.R.C.P., D.P.H., D.T.M. & H., Senior Health Officer, Federated Malay States, and a preface by SIR RONALD ROSS, K.C.B., K.C.M.G., F.R.C.S., D.P.H., M.D., LL.D., D.Sc., F.R.S., NOBEL LAUREATE. Second edition. Pp. 381; 115 illustrations. New York: E. P. Dutton & Company, 1921.

FEW who have not actually lived in the tropics realize the magnitude, the importance, or the complexity of the problem of malaria prevention in these lands. Twenty years of study and successful effort have qualified the author to speak with authority upon the subject of mosquito control in the Malay States. He pictures the problems which faced him as a member of the Malaria Advisory Board appointed by the British government, and as health supervisor of rubber estates scattered over an area twenty times as great as the Panama Canal Zone. He describes in minute detail the attempts which were made to solve these problems, his failures and his successes, and records the observations which he made at the time.

This work will stand as one of the milestones in the history of malaria control and the book is therefore of interest from the historical standpoint. To those confronted with the problem of mosquito control in the tropics it will be an invaluable aid, and wherever the drainage problem has to be met in our war upon the mosquito it will be of value as a reference book. The last five pages give the author's conclusions and are well worth reading by anyone interested in the prevention or treatment of malaria.

J. H. A.

OPIATE ADDICTION: ITS HANDLING AND TREATMENT. By EDWARD HUNTINGTON WILLIAMS, M.D., formerly Associate Professor of Pathology, State University of Iowa; Assistant Physician, New York State Hospital System; Special Lecturer on Criminology and Mental Hygiene, State University of California. Pp. 194. New York: The Macmillan Company, 1922.

HARDLY a page of this brief treatise is without its human interest and practical value. The various methods of rapid withdrawal, including those popularized by Lambert, Bishop, and others, are outlined with admirable clarity. The author discusses the gradual withdrawal of opium even more fully and in a manner which will appeal to the practitioner who needs help in the management of his addiction cases. The pages reflect the author's intimate knowledge of the language and habits of the underworld, and of the operation of the Harrison Law. In this connection it is regrettable that the reader is not informed regarding the modus operandi by which dope peddlers secure the drug, since here must be the point of attack if the illicit traffic is to be stamped out.

J. H. A.

RADIUM THERAPY. By FRANK EDWARD SIMPSON, A.B., M.D., Professor of Dermatology, Chicago Polyclinic; Adjunct Clinical Professor of Dermatology, Northwestern University Medical School; Director of the Frank Edward Simpson Radium Institute. Pp. 391; 166 illustrations and 30 tables. St. Louis: C. V. Mosby Company, 1922.

THE limitation of space precludes full consideration of this important volume. The author has presented the results of his vast experience with the physical, experimental, biological and therapeutic aspects of radium in a concise and comprehensive style. In addition, the volume gives evidence that the author has thoroughly studied the literature bearing upon radium, its application and effects, as he has quoted frequently from an extensive bibliography. The book is a valuable contribution to the literature of radiology and should be owned and studied by every internist and general surgeon.

In Chapter XIII, in which the author considers the important subject of dosage, valuable tables are given together with thorough explanations. Chapter XV, dealing with the application of radium in general surgery, is admirably presented, but it might be mentioned that there is some difference of opinion among eminent authorities as to the best time to operate following preoperative radiation.

On the whole the book is logically arranged, with clear readable type, and contains an abundance of excellent illustrations.

E. P. P.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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A Graphic Method for Calculating Woodyatt Diabetic Diets.—HANNON and MCCANN (*Bull. Johns Hopkins Hospital*, 1922, **33**, 119), after a brief discussion of Woodyatt's practical application of Shaffer's work on antiketogenesis, present a graphic chart which has been found of great service during the past year at the Johns Hopkins Hospital in facilitating the preparation of diabetic diet prescriptions. Starting with the patients' estimated caloric requirement, with the aid of their chart a maintenance diet may be rapidly worked out which will supply the desired percentage of protein and at the same time preserve a safe balance between the ketogenic and antiketogenic substances found in the diet. They also point out the fact that a diet containing less protein permits the use of much greater amounts of free carbohydrates.

The Toxicity of Botulinus Toxin by Mouth.—BRONFENBRENNER and SCHLESINGER (*Jour. Am. Med. Assn.*, 1922, **78**, 1519) state that botulism, a comparatively rare disease in this country, is apparently increasing in prevalence. The disease is caused by eating food contaminated with botulinus toxin. This toxin, elaborated by Bacillus botulinus, is quite analogous to the toxins of tetanus and diphtheria. They resemble one another in many respects, but differ quite markedly in others. The toxin of Bacillus botulinus is analogous to other toxins in all the essential properties, identifying it as a true bacterial toxin. It can be isolated from cultures by filtration. It kills experimental animals in small doses with symptoms characteristic of the disease. It is thermolabile and it is neutralized by a specific

type antitoxin. In the case of Bacillus botulinus one is dealing with a group of bacteria, the members of which are capable of producing the same symptoms, and which have similar cultural characteristics, but which are different in their immunological reactions. Experimentally botulinus toxin is many times more potent than either of the analogous toxins. The symptoms of botulism appear after a period of incubation, but this period is a matter of minutes as compared to hours in the case of tetanus and diphtheria. Neither tetanus nor diphtheria toxin is poisonous when taken by mouth, whereas botulinus toxin is toxic when taken by mouth in very small doses. The toxins of the first two bacteria are destroyed by the digestive processes which go on in the stomach and duodenum. The botulinus toxin, however, resists the acidity of the stomach for many hours, and, furthermore, trypsin and pepsin have no destructive effect upon it. In view of the experiments carried on by the authors one must conclude that the placing of crude filtrate in the stomach consists essentially in an acidification *in vivo* with a resulting increase in potency similar to that which can be accomplished by acidification in a test-tube. The failure of the digestive processes to alter the toxin enables direct absorption to occur through the digestive tract. Besides differing from other bacterial toxins in that it is toxic by mouth, botulinus toxin differs from them in its reaction with ethyl alcohol. Precipitation of tetanus and diphtheria toxin with alcohol produces a very refined substance, while the botulinus toxin by precipitating it with alcohol is destroyed. In several recent outbreaks of food poisoning some of those exposed escaped altogether or had very mild symptoms. The investigators of the outbreaks discovered that those who had escaped symptoms had partaken rather freely of alcoholic beverages during the meal.

Pituitary Extract Intranasally in Diabetes Insipidus.—BLUMGART (*Arch. Int. Med.* 1922, **29,** 509) describes a method of administering pituitary extract by intranasal spray, thus avoiding the necessity for frequent hypodermic injections in cases requiring continued treatment. Extract of the posterior lobe of the pituitary sprayed intranasally in a case of diabetes insipidus was found to check the polyuria and polydipsia as effectually as did hypodermic injection. Administration by mouth or rectum proved quite ineffectual. Given by mouth in tablets coated with phenylsalicylate the extract was likewise without effect. Histamin failed to modify thirst or polyuria, no matter how given. The exact mechanism of absorption is undetermined. It is pointed out, however, that there is an almost direct communication between the lymphatics of the nasal mucosa and the subarachnoid space.

Hypophysectomy in Dogs and Cats.—CAMUS and ROUSSY (*Compt. rend. Soc de biol.*, 1922, **86,** 1008) describe the technic of the buccal route and of the temporal route used by them in approaching the hypophysis. The operative mortality was high from meningitis, hemorrhage or brain injuries. Some of the animals died within several days, others within several weeks and still others lived for several months. Sixteen animals were sacrificed after a long time and ten or more were still living and apparently well. Total removal of the hypophysis was attempted at

each operation and this was controlled by thorough examination of the material removed at operation and by careful macroscopic and microscopic study of the base of the brain in the animals that died or were sacrificed for study. From their researches they conclude that for adult dogs and cats the hypophysis is not necessary for the maintenance of life.

Emetic Action of Digitalis.—HATCHER and WEISS (*Arch. Int. Med.*, 1922, **29,** 690) showed in their convincing experiments that emesis resulted after the intravenous administration of a digitalis body when the carotid and vertebral arteries were tied, although very little of the poison could have reached the vomiting center. On the other hand perfusion of brain and medulla with defibrinated blood to which euabain had been added did not produce nausea or vomiting, nor was direct application of digitalis bodies to the vomiting center followed by emesis. The application of 0.0001 mg. apomorphin hydrochlorid to the vomiting center, however, was promptly followed by vomiting. Further experiments showed that when the nerve supply of the heart is intact emesis can be produced by the intramuscular injection of a digitalis body, but that these bodies are not capable of inducing vomiting when all of the nervous connections between the heart and the medulla are cut. These results are interpreted as evidence that the digitalis bodies produce emesis by a reflex, protective in nature, from the direct action of the drug on the heart itself. Impulses appear to pass from the heart to the medulla chiefly by way of the sympathetic but to some extent by way of the vagus. Such a conception of the mechanism of the emetic action of digitalis bodies obviously means that the effect of the drug on the heart cannot be dissociated from its emetic effect.

Divided Meals for Severe Diabetics.—GRAY. **Multiple Meals in Severe Diabetes.**—MURAYAMA (*Boston Med. and Surg. Jour.*, 1922, **186,** 23). These authors present cases which show that in some instances at least the use of six or more meals a day instead of three is followed by an increase in the sugar tolerance for severe cases of diabetes. Absolute proof of cause and effect is neither given nor contended, but it is very strongly suggested that the severe diabetic's ability to metabolize food may be stimulated by small meals, frequently given. Gray speculates as to the cause of these apparently gratifying results. His theory of divided meals appears to be activation of the liver or pancreas by a small preliminary meal of carbohydrate given one or two hours before each main meal; the organism, being then in action at the time of that regular meal, responds to the food load more vigorously than with the every-day three-meal schedule. Relevant statements found in a search of the literature are briefly reviewed. The method which is outlined as follows is advocated as having practical value: (1) Intervals between meals, two and one-half hours, never less, except that the first activating meal (the keystone of this technic) may be taken any time between one and two and one-half hours before the regular breakfast; (2) caloric value of meals—of the extras the first must be the smallest meal of the day. Of the main meals the regular breakfast is to be the smallest; (3) composition of the activating meals: practically pure carbohydrate, generally most conveniently administered, as an orange, a grapefruit or 5 per cent vegetables.

SURGERY

UNDER THE CHARGE OF

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Von Recklinghausen's Disease or Osteitis Fibrosa.—YOUNG and COOPERMAN, (*Ann. Surg.*, 1922, **75**, 171) say that osteitis fibrosa is a distinct pathological entity characterized by a fibrous metaplasis of bone. Under this term may be included benign bone cysts, giant cell sarcoma of the epulis type, hemorrhagic osteomyelitis and the generalized form (von Recklinghausen's disease). Two types of the disease are recognized—a local and a general type. Local osteitis fibrosa and benign bone cysts are dependent upon trauma in a great majority of instances. The general form is dependent upon grave nutritional disturbances. Cysts, osteitis fibrosa cystica and giant cells may occur in the same bone. The giant cell content is not prognostic of malignancy. Diagnosis of osteitis fibrosa is based upon the long duration of this process with very vague symptomatology, the frequency of spontaneous fractures and upon roentgen-ray examination. Very often microscopical examination of pathological sections is necessary to clear up the diagnosis. The local form of the disease is benefited by curettage and bone transplant. The type showing multiple lesions must be given constitutional treatment directed toward the underlying constitutional disturbance. If the lesions be accessible curettage and bone transplant may be employed.

The Results of High Ligation of the Cystic Duct in Cholecystectomy.—HARTMAN, SMYTH and WOOD (*Ann. Surg.*, 1922, **75**, 203) say that the cystic duct stump usually dilates to form a pseudo-gall-bladder. We may therefore get a recurrence of the symptoms after a cholecystectomy. Where the cystic duct is ligated flush with the common duct, there is a general dilatation of all ducts, indicating that there is pressure in the biliary system. While the gall-bladder is not essential to life, it seems to have a very definite function of storing bile and acting as a tension bulb to regulate pressure in the biliary system. Nature endeavors to restore the normal condition in the biliary system after the removal of the gall-bladder by dilating and enlarging the ducts including the cystic duct stump.

A Comparative Analysis of 213 Forearm and Leg Fractures.—BIZARRO (*Ann. Surg.*, 1922, **75**, 221) says that backfire is one of the commonest causes of forearm fracture and slipping or twisting the ankle the commonest mechanism of leg fracture in these series. Fracture of the radius alone is the commonest in the forearm and fractures of both tibia and fibula commonest in the leg. The radius was fractured in 84

per cent of cases of forearm (single and double) fractures and the fibula was fractured in 79 per cent of cases of leg (single and double) fractures. The lower third of the radius is the most fragile part of the bone and was fractured in 91 per cent of single radial fractures and the lower third of the fibula is the weakest point of the bone and was fractured in 88 per cent of single fibular fractures. The upper end of the ulna is the commonest seat of single ulnar fractures and the lower third of the tibia the commonest place of single tibial fractures. The lower third of the radius and ulna is the commonest seat of double forearm fractures and the lower tibial third, the commonest level of the leg double fractures. The classic fractures of Colles, Pott, Dupuytren, as conceived by these authorities are comparatively rare. Epiphysial fractures are commoner at the wrist. The marginal fractures of the radius (Barton, Letenneur) are rarer than the marginal tibial fractures. Longitudinal or medullary splits are commonest in the fibula. Chauffeur's fracture may occur at the upper end as well as at the lower end of both radius and ulna. The commonest direction of the fibular fractures is from before backward and upward and is usually incomplete. Fractures of the tubercle appear to occur in a growing bone and fractures of the tibial tuberosity in an adult bone. Fractures of the upper half of the ulna, radius, tibia and fibula diaphysis are usually due to direct trauma.

Duodenectomy (An Experimental Study).—MANN and KAWAMURA (*Ann. Surg.*, 1922, **75**, 208) say that their experiments show that the duodenum is not necessary for life and the fact that noteworthy changes were not observed makes it appear that its function does not differ greatly from that of the rest of the intestinal tract. Only one positive finding was obtained. In two of the dogs a large ulcer was found on the jejunal side of the suture line of the gastrojejunal anastomosis. In one of the animals the ulcer perforated, causing peritonitis and death. Since peptic ulcer of the subacute or chronic type is very rare in the dog, it seems significant.

The Treatment of Fractures.—SMITH (*Brit. Med. Jour.*, April 2, 1921, p. 483) says that conservative treatment by splinting has again come into its own purely on account of the excellent results gained by standardized methods in thousands of gunshot compound fractures obviously unsuitable for operative fixation of the fragments. Where experience tells one that good functional results cannot be obtained by splinting alone, we should be prepared to operate, provided we have experience in that method also. The main essential is that, following general principles guiding treatment, we shall pay the strictest attention to details in whatever method we adopt. The author advocates the principles laid down by H. O. Thomas and Sir R. Jones in the mechanical treatment of fractures, namely, a fracture is a potential deformity and must be regarded as such. Strong, steady, fixed extension with corresponding counterextension is required, as distinguished from forcible, intermittent pull succeeded by a period of muscular relaxation; correct alignment in conjunction with obliteration of shortening; avoidance of rigid, circular compression, which tends to produce ischemia. Union may be delayed—this is sometimes unavoidable; but there is a vast difference between delayed union and non-union.

Union of a fracture does not imply its consolidation. Both mal-union and non-union are common occurrences and are often related. In fractures of the neck of the femur the angle between neck and shaft is reduced and a condition of coxa vara results. In fracture of the upper third of the shaft the upper fragment is abducted, the lower fragment pulled up to the inner side of the upper one, and a shortened, bowed femur results. In fractures of the middle of the shaft there is a concavity forward instead of the normal convexity. The same deformity is present in the lower fourth of the shaft. Fractures in upper third of the leg may lead to a high bow-leg. Fractures of the middle third may result in knock-knee with either inversion or eversion of the foot. Fractures of the lower end of the lower third of both bones generally end with a valgoid deformity of the foot with an internal rotation. These are the commonest reasons for mal-union: being too sparing with traction; inefficient splinting, and the effect of allowing body weight to fall on recovering bone too soon. If there be pain over the site of a fracture of old standing, especially on digital pressure, unsound union may be suspected, and if this pain be accompanied by an exuberant callus formation the diagnosis is absolute. Some fractures are slower than others in beginning to unite. Too much interference in the way of constantly moving the fragments to see whether union is occurring is apt to end in non-union. In comminuted fractures the wholesale removal of bone fragments is apt to result in non-union also. Treatment by what Thomas called damming and hammering is of assistance. In fractures of the lower extremity, operation should be postponed until the effect of the patient getting about with the aid of an appliance has been tried, for the number of stubborn non-unions that respond to this simple procedure is surprising. The need for operation having arisen, the question whether this should consist of freshening the fractured ends and bone-plating or bone-grafting is one which depends upon personal choice. Likewise, the question what fractures should be treated at once by operation, and which by splinting, must be answered by the individual surgeon. The author generally operated on spiral fractures of the lower third of the leg by means of inlay grafts, but plating is equally satisfactory in skilled hands. Fractures of the patella in transverse axis are treated by wiring, as are also fractures of the olecranon where there is a large gap with rotation of the fragments. Scaphoid fractures are also operated where the proximal fragment prevents full hyperextension of the wrist and where there is palmar dislocation of the semilunar bone; removal of the proximal portion of the scaphoid is generally sufficient. All other fractures are treated by means of splinting or posture or both combined in some cases with rigid extension and counterextension. Fractures of the neck of the femur and the upper fourth of the shaft are best treated in the double Thomas frame with extension straps on both legs, the affected limb being widely abducted. The groin on the sound side gives adequate counterextension. In old people it is advisable to fit a walking caliper, made one-half inch too long, and allow the patient up on crutches. Careful nursing is essential in cases treated on a frame: the back must be carefully rubbed with talcum twice daily—the flat of the hand being carefully interposed between the skin of the back and the pad of the frame; an alcohol rub twice weekly is also necessary; with these rules strictly

obeyed, no skin trouble need be feared. Fractures of the middle and lower portions of the shaft of the femur, fracture of the condyles and fractures of tibial tuberosities and shaft in the upper three-fourths are all treated in the Thomas knee-bed splint. The use of calipers, ice-tongs and Steinman's pins to produce traction are complications which are only applicable in hospitals, in the hands of experts, and in a large percentage of cases are unnecessary. Fractures of the leg, with the exception of Pott's fracture, are treated on the same lines, and fractures involving the knee-joint require adequate restoration of fragments by manual pressure combined with traction. The reduction of a Pott's fracture is of greater importance than the splinting. Forcible traction with the foot in extreme extension, combined with a downward pull on the leg and an upward pull on the heel to reduce the backward displacement of the foot, should reduce the deformity, but occasionally it is necessary to divide the tendo Achillis. The foot is then forcibly inverted into an overcorrected position. In fractures of the tarsus, when reduction is complete, all that is necessary is for the foot to be kept at a right angle. Fractures of the humerus in the region of the shoulder-joint, if inefficiently treated, show limitation of abduction and external rotation. Fractures in the region of the elbow-joint are apt to result in defects of flexion and supination: supination is often deficient in fractures of both bones of the forearm; the deformity of a mal-united Colles' fracture with limitation of wrist movement, of pronation and supination and of finger flexion is well known. Fractures of the anatomical neck of the humerus are best treated by a wrist sling which allows the weight of the arm to act as an extension, with a pad in the axilla to produce slight abduction of the upper arm. In treating separation of the upper humeral epiphysis, in childhood or adolescence, it is advisable to abduct the arm to a right angle and to rotate it outward until the hand is level with the mouth, and then to immobilize the arm in this position either by one of the humerus abduction splints or in plaster. Impacted fractures of the surgical neck are best reduced by the method of Thomas: The patient is seated upon a chair and a roller-towel is passed under the axilla and fastened to a coat-hook or nail; a wrist sling is fastened around the neck and a clove hitch is made fast to the elbow, with a long loop which comes to within a foot of the floor and which acts as a stirrup for the operator's foot; extension is obtained while both hands of the operator are free for manipulation; the axis of the pull is brought to the abducted position, and when reduction appears complete the arm is forced upward and reimpacted; treatment is same as that for the anatomical neck except that a larger axillary pad is indicated. Fractures of the shaft are treated by malleable-iron fracture splints which can be bent to cover in the shoulder-joint and thus produce fixation. All fractures in the region of the elbow-joint, with the exception of the olecranon, are treated after adequate and complete reduction in the Jones' or full-flexed position; this position cannot be obtained unless reduction is complete. Whether the fracture is supracondylar, T-shaped or intercondylar, one must reduce by traction-extension, supination and hyperflexion. If this latter is not obtained the routine must be repeated until it is, and then the arm must be kept in this position at rest for at least three to four weeks. The author gives warning against passive movements after the

arm is being gradually brought down, otherwise traumatic arthritis and consequent stiffness of the elbow ensue. For this type of fracture the rectangular internal splint should be abolished. Fractures of the head and neck of the radius must be fixed in full supination, otherwise limitation of this movement will certainly result. Fractures of the shaft of both bones require consideration of two important points: first, the shaft of the ulna must be kept straight, and secondly, the curve of the radius must be conserved, as the whole length of the posterior border of the ulna is straight, and on this the curved radius rotates like a bucket-handle. Nearly all neglected fractures of the forearm show limitation of supination, whereas pronation is not defective. Colles's fracture requires complete and adequate reduction before splinting takes place. The Jones method is preferable to the handshaking plan, because the force is applied directly to the bone instead of working through the carpal bones. Twisted fracture splints, adequately padded, to keep the replaced fragments in an overcorrected position and the hand in ulnar deviation, are applied and remain for four weeks, movements of the fingers and thumb being allowed from the first.

PEDIATRICS

UNDER THE CHARGE OF

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Nephritis in Children.—BOYD (*Am. Jour. Dis. Children*, 1922, **23**, 375) holds that the most common etiological factor in nephritis is an acute infection. Cases of nephritis in childhood may be divided into the following classes: (*a*) Acute glomerulonephritis, (1) resolving, (2) nonresolving; (*b*) chronic glomerulonephritis; (*c*) nephrosis. The acute cases which recover are differentiated from the nonresolving type by (*a*) a better response to renal function tests; (*b*) by a steady and rapid improvement clinically; (*c*) by a rapid diminution and complete disappearance of the albuminuria. The chronic cases differ in the history of past symptoms and signs attributable to the kidney, especially nycturia, in the presence of more numerous casts in the sediment. Relapses recur frequently in the more severe cases and of themselves justify a bad prognosis. Tests of renal function give invaluable aid in determining the prognosis, as well as the line of treatment. The concentration test and the determination of the blood nitrogen constituents furnish the most reliable data. Consideration of the responses to functional tests coupled with clinical observation enables one to foretell fairly accurately the outcome in individual cases. Administration of calcium salts, particularly the lactate, is of definite value in clearing up the edema. Pathologically the most common lesion in the acute cases is a glomerulonephritis of the intercapillary type, accompanied by more or less degeneration in the cells of the convoluted

tubules. The chronic cases showed the same lesions as the acute cases plus searing and fibrotic changes. In the nephrotic cases tubular changes predominated.

The Breast-fed Pellagrin: Relation to the Avitaminoses.—LUSTBERG and BIRCHETT (*Arch. Pediat.*, 1922, **39**, 254) eliminate the specific infectious theory as the causation of breast-fed pellagra. In treating in their institution more than 50 cases a year of men, women and children without segregation there never has developed a case among the other patients or among the help. The manifestations of the disease in both mother and child present themselves in the spring and summer. A dietary error shown to be pre-pellagrous was prevalent in the winter diet of the mother. A pre-pellagrous diet, such as dried beans, dried peas, corn-meal, lard and canned evaporated milk, contains an excess of carbohydrate and lacks protein. This diet is unbalanced and it has excess foodstuffs shown to be poor in vitamines, and further it has not the proteins, a foodstuff which has been shown to be rich in vitamines. The character of this diet undoubtedly influences a baneful effect on mothers' milk, and therefore the suckling infant shares in the deficiencies. Curative results were obtained by placing the infant on artificial food such as cows' milk, fruit juices, vegetables, zweiback and purees. This ration is well balanced and contains vitamines in full force.

Eczema in Breast-fed Infants as a Result of Sensitization to Foods in the Mother's Dietary.—SHANNON (*Am. Jour. Dis. Children*, 1922, **23**, 392) found that eczema in breast-fed babies was a result of sensitization to food proteins contained in the mothers' dietary, and transmitted to the infant through the breast milk in a great majority of cases. Removal of these proteins from the diet of the mother usually results in cure of the condition in the patient. In cases in which all the foods cannot be eliminated from the diet of the mother, limitation of the same will often result in improvement of the eczema, presumably because there is a threshold in the mother up to which the food may be taken without its harmful constituents appearing in the breast milk. Sensitization of the infant may be determined by the cutaneous reaction to the purified proteins. The erythematous reaction at the site of the test is to be considered as indicating sensitization, and being much more common than the wheal, is correspondingly more important. Sensitization is usually multiple, and may be to a majority of the foods in the dietary of the mother. Sensitization to become more widespread in a great many cases as time goes on, due to acquisition of sensitivity to new foods. Repeated exacerbations and failure to cure may be due to a lack of coöperation on the part of the mother, to sensitization so widespread as to make sufficient limitation of the diet impossible, to failure on the part of the physician to test for all foods, to the acquisition on the part of the infant of new sensitization, and to error in the procedure of determining sensitization whether avoidable or otherwise. As general prophylactic measures, it is recommended that all mothers be cautioned to eat a large variety of foods, and a small quantity of any individual article of diet, that eggs be restricted rather than forced in the diet of the mother, and that all cases of eczema be

studied early and that offending foods be eliminated before sensitization becomes so widespread as to make limitation of the diet impossible. The proper study of all cases of eczema in breast-fed babies that do not yield promptly to the older methods of treatment requires the determination of sensitization in the infant to all of the foods contained in the diet of the mother and in the event of exacerbation, the frequent repetition of these tests.

Sitting Height and Stem Length in Private-school Boys.—GRAY (*Am. Jour. Dis. Children*, 1922, **23**, 406) feels that height measurements are being rivalled and possibly superseded by measurements of the trunk independent of the legs. The best trunk length seems to be the sitting height at present, as well as the stem length. These measurements are closely similar. In his report these two measurements are taken from 114 picked upper-class school-boys. The sitting height was not constantly parallel to the stem length, for while it averaged one-half inch greater it varied anywhere from being identical in some boys to two inches greater in others. The stem length was found to be easier to measure accurately as there were more constant agreements in repeated measurements. The absolute values both of stem length and sitting height, averaged according to age, showed greater values than any that he was able to find in the literature. This is natural considering the advantages enjoyed by this group of boys, as it is certain that strains of men can be bred as well as horses. The proportional sitting heights, or sitting heights related to stature, were markedly less than those in the literature. This means that well-developed children have longer legs for their heights than children retarded in growth, which may be stated that the principal defect of growth in badly nourished children lies in the lower extremities. The author believes that stem length should replace the sitting height measurement in the fields of anthropology and of school hygiene.

Prophylactic and Therapeutic Value of Pertussis Vaccine.—DAVIES (*Am. Jour. Dis. Children*, 1922, **23**, 423) states that pertussis gained access to his institution through a child who had been exposed before admission. Of 176 children exposed, 114 had not had the disease 20 had had the disease, and the history was inadequate in 42 cases. Thirty-three children developed the disease. Records in 27 of these cases were negative for previous attack and doubtful in the remaining 6. These cases were admitted to the hospital ward with a positive diagnosis of pertussis based upon the clinical findings in the majority of the cases. The remaining 146 children were given prophylactic doses of pertussis vaccine regardless of previous history. After the first 33 cases were removed from the main building only 4 additional cases developed. It is quite sure that the others were exposed to the disease at the time of the greatest infectivity. Most of the children were very young, and the majority had not had the disease. Although it appears that the individual child responds differently to the pertussis vaccine, the duration of the disease is shortened by its administration. The paroxysms were lessened in severity and duration, and whooping and vomiting were obliterated.

The Basal Metabolism of Infants Fed on Dry Milk Powder.—Talbot and Moriarty (*Public Health Reports*, 1922, **724**, 176) found that metabolism studies in their series of cases show a tendency for the males to fall within or very close to the standard variations, the greatest deviation being in the calories per kilogram of body weight. The metabolism of the female infants ran higher, and with few exceptions fell more than 10 per cent, the average, but were not outside of the extreme normal variation. This difference in the metabolism of the different sexes is in accord with what Benedict and Talbot found in their series of observations; that is, that it is much more difficult to predict the metabolism of female than it is of male infants, and that the deviation from the average was much greater in the former than in the latter. The results of the findings of this study on the basal metabolism of infants fed on dry milk powder show either a normal or a slightly elevated basal metabolism. Coincident with most of the cases of an elevated metabolism there was an elevation in temperature to 99° or 100°, but it does not seem that this slight elevation in temperature is sufficient to explain the increase in metabolism. One case had been vaccinated against smallpox six days previous to the metabolism observation. There are no published data on the effect of vaccination on the metabolism, but it does not seem unlikely that the metabolism would be more likely to be increased about the tenth or twelfth day of the reaction rather than earlier. In these studies all precautions were taken to insure quiet periods, and careful and kymograph records were kept of the infants during the metabolism periods to warrant recording the results as purely basal findings. The basal metabolism of this series of infants fed on dry milk powder mixtures tends to be slightly higher than that of average normal infants, but is within normal limits. This may have been due to relatively high protein content of the food, but the deviations from the average are not great enough to permit any striking conclusions to be drawn.

Treatment of Pylorospasm in Infants.—Grulee (*Jour. Am. Med. Assn.*, 1922, **78**, 1183) calls attention to the fact that thick food may cause in infants with pylorospasm a serious febrile reaction followed by symptoms of shock. Because of this he feels that a more physiological method of caring for these patients might be of value. Provided a treatment is effective, its simplicity is a great recommendation. It is frequently necessary to insist on hospital treatment so that the best results may be obtained. There are two indications for treatment of pylorospasm: The first is to relax the spasm at the pyloric sphincter, and secondly to remove the irritation in the stomach resulting from the accumulation of disintegrated food which has remained in the stomach as a result of the pyloric closure for a period longer than the normal. For the first of these conditions the employment of atropine is advised; for the second the cleansing of the stomach and the administration of a food which is adequate but not irritating. In following out these suggestions the author gives atropine hypodermically in a quantity of from 1/1000 to 1/500 grain fifteen minutes before each feeding. Before the food is given, the stomach is carefully washed until the washing returns clear. The food is then given through the tube before it is withdrawn. He nearly always gives a mixture of albumen milk

and a dextrin-maltose combination, a quantity sufficient to meet the needs of a child of like age without gastrointestinal disturbance. In breast-fed babies he allows suckling after the stomach washings. His results in this group of cases is not nearly so satisfactory as in the artificially fed, but he has never felt that it was wise to discontinue breast nursing for this reason. Results appear early and often within two or three days the vomiting ceases entirely, or there is only slight regurgitation. This is followed by a rise in the weight curve. The stomach washings are intermitted and if no relapse occurs, they are finally discontinued and the atropine dosage gradually diminished until it finally reaches zero.

OBSTETRICS

UNDER THE CHARGE OF

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Albuminuria in Pregnancy.—BOURNE (*Brit. Med. Jour.*, April 1, 1922, p. 520) believes that further knowledge concerning albuminuria in pregnancy must be gained by chemical study. Under this title is commonly described a group of symptoms of which the most important is the presence of albumin in the urine; next in importance increased blood-pressure. As far as types were concerned the first and most common is subacute nephritis. The second in frequency is the cerebral type, where convulsions occur in labor, often without premonitory symptoms except the presence of albumin in the urine. The third type which he describes is the gastric type, characterized by uncontrolled vomiting, occasionally seen in early pregnancy. This he considers as really of hepatic origin. The fourth class is the hepatic condition which he finds rare; and the fifth, the so-called uterine type with necrosis of the uterine wall and serious hemorrhage. In 4000 cases of pregnancy and labor, 30 per cent had some degree of albuminuria. Unless high blood-pressure, vomiting or other symptoms develop, albuminuria alone is not important. Convulsions indicate serious danger, and 46 per cent of patients, having albuminuria have convulsions. When these patients do badly, it is in one of three ways; by convulsions or by the complete suppression of urine, due to necrosis of the cortex of the kidney, or by the development of jaundice. The number of convulsions had no direct relation to the mortality. Where patients were suffering from toxic albuminuria, it was especially serious if fresh symptoms appeared during medical treatment, or if the symptoms already present suddenly became intense.

HOLLAND, studying the after-condition of patients who had eclampsia and albuminuria, found that a considerable percentage of them showed signs of chronic kidney damage afterward. He believed that labor should be induced in all such cases.

WALLIS, studying the blood and urine, found that after the fourth

month the blood-urea and blood-sugar were less than in the normal non-pregnant woman. The quantity of diastase was increased. In the toxemia of pregnancy blood changes were slight: Cholesterol was increased, especially in cases of eclampsia; in the urine a high diastase percentage preceded albuminuria. He would distinguish between the toxemia of pregnancy and a true nephritis in pregnancy by the estimation of urea in the blood and diastase in the urine. WILLCOX considered the corpus luteum an important factor in producing toxins. He believed that the toxins produced in pregnancy damaged the organs of excretion in each succeeding pregnancy.

The same discussion before the Harveian Society is reported by the *Lancet*, April 1, 1922, p. 651. In reporting Bourne's paper it is stated that in 18,000 cases of labor at Queen Charlotte's Hospital, but 3 cases of the hepatic form of toxemia have been observed. Eclampsia can occur with comparatively low blood-pressure, as cases are reported where the blood-pressure was below 160 mm. The mortality curve of all toxemic patients was 5 per cent; where the blood-pressure was 150 mm. or below the mortality was 9 per cent; where it was 190 or above, the mortality was 27 per cent. Holland is quoted as stating that at least 12 per cent of eclamptic patients suffered permanent damage to the kidneys.

Pneumonia in the Newborn.—(*Brit. Med. Jour.*, March 25, 1922, p. 469), BROWNE publishes a paper upon pneumonia in the newborn. In 80 cases of infantile death in the Royal Maternity Hospital, Edinburgh, there were 21 or 26.25 per cent in which the cause of death was found to be pneumonia; 11 were in premature and 9 in full-time infants, the ages varying from eight hours to five weeks. The fact that so many of these cases were premature, shows that the premature infant is especially liable to infection. It is estimated that the premature infant is fourteen times as liable to die from pneumonia as is the infant born at full time. It is also of interest to know that 5 of these infants were syphilitic, another probably so, while 1 had fracture of the supraorbital plates with extradural hemorrhage overlying them. One of the syphilitic cases had an extradural hemorrhage in the spinal cord. Among the premature infants were many with areas in the lungs, where the lungs had not expanded; in some involving part of one lung and a large part of the other. It seems probable that this condition predisposes to pneumonia. There were 2 very instructive cases of premature rupture of the membranes, followed by pneumonia in the infant. In 1 the pneumococcus was present, in the other the Bacillus coli communis. One of the mothers was delivered by forceps, and the other had induced labor. Both mothers made uninterrupted recoveries, and evidently the children died from infection, developing before or during birth. Of the pathology of the condition, there were 11 cases of the ordinary catarrhal pneumonia, 1 with pleural effusion, 2 with empyema.

There were 2 cases of interstitial pneumonia with catarrhal pneumonia added. In 1 case of catarrhal pneumonia there was hemorrhage into the bronchial tubes and into the lungs. In 5 cases there was acute congestion and edema of the lungs with hemorrhage into the lung substance. In 1 case there was both insterstitial and catarrhal pneu-

monia and hemorrhage, and in 1 interstitial pneumonia with congestion and hemorrhage. The catarrhal pneumonias were in a fairly advanced stage of consolidation. It is sometimes difficult on examining the lung to distinguish precisely between the different varieties.

Among new-born infants pneumonia is a common cause of death during the first week of life, and occurs in 26 per cent of new-born children. It may be caused by infection before birth, following premature rupture of the membrane, and at the time of birth the child may be in an advanced stage of pneumonia. The child has very little defensive reaction against infection as compared with the adult. In the first few days of life pneumonia is an exceedingly insidious disease; generally presenting no characteristic symptoms which might lead to its presence being suspected or established on physical examination. The microscopic examination of the lungs may be necessary, and the postmortem examination in the ordinary manner may fail to make a diagnosis. The acute hemorrhagic pneumonia of infants is a distinct condition. In this condition children, previously apparently healthy, either full time or premature, may die suddenly. This death is preceded by acute congestion of the lungs, followed by hemorrhage from the rupture of fragile blood vessels. Very often sudden death is preceded by nosebleed, pallor and it is thought that the cause of the accident may be something in the nature of an anaphylactic action. Two precautions are imperative in the interest of new-born children: the avoidance of premature rupture of the membranes during labor and the taking of every precaution to protect the child against infection.

Osteomalacia with Rupture of the Uterus.—SCHOCKAERT of Louvain (*Gynécologie et obstétrique*, 1922, Tome 5, No. 2) describes the case of a patient aged forty years in her seventh pregnancy, in labor several days. She was brought to the Maternity at Louvain in miserable condition. The history showed the usual diseases of childhood, that menstruation appeared at seventeen and had always been regular. The six preceding pregnancies had terminated normally. Three children were living and in good health; 2 had died; 1 from some affection of the digestive tract, associated with alterations in the bone probably rachitic; the other had died of angina.(?) The patient had been ill three years; before her sixth pregnancy she had suffered from continuous pain in the lower extremities, especially in the thighs and knees. It had become impossible for her to flex the leg upon the thigh and the thigh upon the pelvis. Later, pain developed among the lower ribs and this became so excessive that the patient made no effort to speak or laugh, and finally pain became severe in the region of the symphysis pubis. Little by little the whole skeleton with the exception of the bones of the cranium had become painful. The patient was pregnant, and during the pregnancy she had grown rapidly worse, to a degree that she could not walk on account of her suffering. Her labor had taken place spontaneously without medical attention and the child had been born alive and survived. After the birth of this child the patient still suffered with pain and could not move without assistance. She remained in that condition until the beginning of the present and succeeding pregnancy. From the history it seemed evident that the physician who had been called to treat her had considered her to be

suffering from rheumatism. This was exceedingly unfortunate, for if the ovaries had been promptly removed at this time, the progress of the disease might have been checked. At about the third month of the seventh pregnancy the patient was unable to walk. Pain became almost intolerable. Her pregnancy continued however, until she was practically at term. She was without medical attention and supposed to be suffering from rheumatism. Three or four hours before she was brought to the Maternity her labor pains began and increased steadily in intensity. The patient could not describe accurately what had happened, and the third day she called a physician, who examined her and ordered her sent to the hospital. On admission the patient was desperately ill, with pulse 140, frequent and shallow breathing and temperature 102° F. She suffered intense pain when touched on any part of the body. The abdomen was enlarged, the uterine tumor falling toward the right. It was difficult to make out the child, but the back seemed to be in front, the head towards the left flank. The different fetal parts seemed to be very superficial. No heart sounds were present and examination suggested that the uterus had ruptured. On attempting to make a vaginal examination it was discovered that the pelvis had assumed the characteristic shape of osteomalacia. The rami of the pubes were very close together; the sacrum was projecting and curved; the cervix uteri was soft and the placenta could be felt, but no fetal part. Exuding from the uterus was a brownish bloody fetid fluid. Abdominal section showed blood in the abdomen, amniotic liquid and a dead fetus lying among the intestines. The placenta was still in the uterus and the uterus had ruptured. Apparently this had occurred at least two days before. The child was somewhat macerated. A Porro operation was rapidly done and a strand of gauze passed for drainage through Douglas' cul-de-sac. The patient did not long survive the operation.

GYNECOLOGY

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Histogenesis of Ovarian Tumors.—The question of the histogenesis of ovarian epithelial tumors, both solid and cystic, has been the subject of much discussion. In view of the wide variations in opinions any evidence that will at all tend to help in the classification of these common and clinically important tumors and that may tend to indicate their origin is of sufficient value to make a record of it, as has been done by Geist (*Am. Jour. Obst. and Gyn.*, 1922, **3**, 231). His studies are

based upon a patient, fifty-two years of age, in whom the ovary on one side presented a typical adenocarcinoma and on the other side a process involving the greater portion of a somewhat enlarged ovary that also resembled a new growth. It is composed of masses of cells, varying in number, either isolated or in large branching strands. The cells in these solid masses resemble the granulosa layer of the follicle. In these masses are found cysts of varying sizes lined by cells of a cuboidal, columnar or the high cylindrical type as seen in the pseudomucinous type of ovarian cyst. Often in these cysts are found oval granular bodies which on superficial examination might be taken for degenerated ova but which are undoubtedly degenerated tumor cells or secretion masses. The origin of this process is the point of interest. It seems to be independent of the tumor of the other side, first, as it bears no histologic resemblance to it, and, second, as it has none of the distinguishing criteria of a malignant tumor. The stroma resembles that of the unchanged ovary and is a predominant part of the process. The stroma and cells always maintain a definite relationship and at no point is there a proliferative or invasive tendency or an inflammatory infiltration. Mitoses are not found. The cells composing the tumor resemble in their appearance and arrangement the granulosa cells and the general structure of the growth in parts suggests the developing follicle with many variations. Because of this morphologic appearance, the arrangement of the tumor and the wide variation in its structure it is suggested that a cell of great potentiality must play the role of originator. In addition, the development of cysts which form by degeneration of the larger cell masses and grow by coalescence suggests this as one method of development of the microcysts and later of the larger cysts that occur in the ovary. Furthermore, the cells lining these cysts are often cuboidal, and occasionally high, cylindrical, mucin-containing elements can be traced by direct observation from the large cell masses of granulosa-like cells. This leads Geist to the presumption that some of the so-called simple cysts, follicular cysts and even the more complex pseudomucinous cysts may be the products of these same embryonal remains. The nomenclature employed for the classification of this type of tumor is still indefinite, as each writer has selected a name that has fitted his theory of origin or the fancied resemblance to some structure of the ovary. At the present time there are tumors similar to the one above described that have been termed adenoma of the Graafian follicle, folliculoma malignum, carcinoma folliculoides, oöphoroma folliculare and folliculoma. Several of the names can be discarded, such as adenoma of the Graafian follicle, folliculoma malignum and carcinoma folliculoides, as the tumor is neither a malignant tumor nor an adenoma. Geist believes that the best way to classify these tumors is not to give them a name but to group them as tumors arising from persistent embryonal structures.

Hemorrhage from Ruptured Corpus Luteum.—Intraperitoneal hemorrhage may arise from various sources, most often from a ruptured ectopic pregnancy. Aside from hemorrhages of a purely traumatic origin, such as ruptured liver, kidney, spleen or pancreas, spontaneous rupture of the uterus may be mentioned. Very rarely, exceedingly serious intra-abdominal hemorrhage occurs, traceable to none of these

sources, but either to a ruptured Graafian or atretic follicle or to a ruptured corpus luteum. A survey of all the available literature on intra-abdominal hemorrhage from ruptured corpus luteum impressed MOORE (*Ann. Surg.*, 1922, **75**, 492), who reports such a case, with the fact that in none of the cases reported, so far as he had been able to ascertain, was the correct diagnosis made before operation. The reason for this is quite apparent: intra-abdominal hemorrhage following rupture of the corpus luteum is a rare occurrence compared with the other pathologic conditions which present an almost identical picture, and it is only natural that the diagnosis which most often fits a condition should be the one made. In general the reports show that the symptomatology of this condition is characterized by sudden abdominal pain, cramp-like or colicky, followed almost always by nausea and vomiting. There is nothing characteristic about the temperature and pulse. Localized abdominal pain and tenderness, generally on the right side, are noted almost immediately after the onset of the sudden pain. Frequently abdominal rigidity and distention are present. The patient is pale, but seldom seems to be in shock. While these symptoms in a woman are characteristic of trouble in either the appendix or Fallopian tube, the possibility of a hemorrhage from the ovary must be considered, especially if the patient shows a marked degree of pallor or anemia. If the menstrual history has been normal and if the patient has had previous intestinal disturbances simulating appendicitis, it is quite natural that a preoperative diagnosis of acute appendicitis should be made. As soon as the abdomen is opened and it is found to be filled with blood, the surgeon decides that the case is a ruptured tubal pregnancy. A rapid search, usually through a right rectus incision, fails to locate bleeding from either tube. Further examination shows the bleeding to be coming from the ovary. Sometimes the condition is complicated by the presence of acute or chronic appendicitis, but often the appendix is found to be normal. The ovary should be considered an aggregation of follicles, some maturing and some retrogressing, constantly changing their appearance and function from day to day. The structures surrounding the different follicles also change, depending on the development and special function of the follicles. The ovarian stroma with its nerves and bloodvessels forms the framework for housing these follicles. Each follicle seems to have a life cycle of its own. All appear alike during their early development, but each month one gradually outstrips the others in growth and develops into a Graafian follicle. Whether this follicle is always different from the others, or whether because of its richer blood supply it grows faster, is not known. At any rate, the ovum of this largest follicle, called the Graafian follicle, is the only one which matures and when ripe is extruded. As soon as this takes place there is no further growth of the other follicles which started to mature; their ova die and gradually disappear, leaving the so-called atretic follicles. Only one ovum grows to maturity each month. Following the giving off of the ovum great changes occur in the Graafian follicle, producing what is known as the corpus luteum. The maturing follicle receives its blood supply from vessels in the theca interna, from which tiny offshoots penetrate into the granulosa. The earliest stages of the corpus luteum are marked by a great increase in the number and size of these vessels in the theca and also at the base of

the granulosa. This fact is of particular interest, since it seems to indicate that, due to the stage of hyperemia which follows extrusion of the ovum, hemorrhage can occur more readily into a corpus luteum than into a Graafian follicle. To the physician who has not seen an abdomen filled with blood exactly as it is found during a ruptured ectopic pregnancy, it does not seem possible that such an extensive hemorrhage could come from the tiny vessels which encircle the follicles, but this has been proved on numerous occasions by surgeons who have actually seen the blood coming from the ovary and also in some instances by microscopic sections which demonstrated the origin of the bleeding.

Prognosis of Cancer of the Cervix.—SKEEL (*Am. Jour. Obst. and Gyn.*, 1922, **3**, 252) has made a collective review of the statistics relative to cancer of the cervix from numerous clinics, and after a thorough digestion of his material he states that two things stand out with increasing distinctness: First, the mortality rate from operation goes down with increasing experience. Thus many writers refer to their last 30 or 50 or 100 cases when stating the possibilities inherent in the Wertheim operation. Second, the operative recovery rate and freedom from recurrence are enormously increased by early diagnosis and early operation. Though the data do not justify so high an operability rate, so low a general mortality rate, nor so high an absolute curability rate, he presents in round numbers what has happened at the expiration of five years to 100 women with cancer of the cervix, if 50 per cent were operable. There would be only a 10 per cent mortality rate and there would be 20 per cent of absolute cures. Out of 100, 20 would be well, 50 inoperables would have died, all presumably having had a Percy cauterization, or some other form of local treatment; 5 of the 50 operated upon died at once and the remaining 45 died from a recurrence. Of the 50 who underwent a tremendously severe operation, 30 were dead within five years. Were the operation less serious, less heroic, and less frequently complicated by postoperative sequelæ, such a showing might be justified; but with the reverse true, the author believes that it lacks justifiability when performed upon the present indications of operability. He concludes that any expectation of an increased number of cures of cancer of the cervix by surgical methods must be based upon earlier diagnosis and panhysterectomy should be reserved for cases in which a positive diagnosis can be made only with the microscope. The parametrium being free so far as digital examination can determine, but the case being far enough advanced to be diagnosed clinically, a high cautery amputation of the cervix, followed by radium treatment, offers the greatest hope of cure. The advanced surgically hopeless case should be treated, according to the author, by radium rather than with the knife, curette or cautery, chemical caustics or Percy cauterization, unless profound toxemia or serious infection contraindicates local interference of any kind.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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A Study of the Gonococcus and Gonococcal Infections.—With the idea of devising improved methods of diagnosis in gonorrhea and of determining whether typing of strains of gonococci could be made, COOK and STAFFORD (*Jour. Infect. Dis.*, 1921, **29**, 561) performed various investigations with stock cultures of gonococci, attempted to isolate fresh cultures from acute cases of anterior urethritis in men and chronic cases in women, and conducted certain immunity tests in gonococcal infections. The stock cultures of gonococci were found to grow satisfactory for routine work on testicular agar, while chocolate blood testicular agar proved to be useful for increasing the vitality of a weakly growing culture. Increased atmospheric moisture but not a reduced oxygen tension were environmental requirements of the organism. Isolation of cultures from acute cases of anterior urethritis in men was most successfully accomplished on chocolate blood testicular agar. No pure cultures of gonococci were obtained from chronic cases of gonorrheal endocervicitis, although single colonies were found on plates of hydrocele testicular agar containing certain members of the triphenyl methane series. The complement-fixation test served only as an aid in diagnosis, being considered by the authors as confirmatory evidence rather than as an independent basis of diagnosis. It was of little value in early cases. A nonspecific reaction was obtained on the intracutaneous injections of a preparation of gonococci. No typing of strains followed the use of complement-fixation and agglutination reactions or by means of the method of absorption of agglutinins.

Absorption from the Peritoneal Cavity.—BOLTON (*Jour. Path. and Bacteriol.*, 1921, **24**, 429) conducted extensive observations on the mechanical and physical factors concerned in the process of absorption from the peritoneal cavity of cats, paying especial attention to the paths by which the absorption is accomplished. That there was a total and uniform rate of absorption of fluid from ascitic cats was determined by injecting it into normal cats and observing the quantity remaining at varying intervals, along with the concentrations of solids. By the use of such colloidal dyes as Congo red, cloth red and Congo blue it was found that each diffused directly into the bloodvessels, but at a slower rate than in the case of crystalloids. In studying the lymphatic paths of absorption, by injections of colloidal silver, it was found that the anterior mediastinal lymph glands were first to be stained, as were the diaphragmatic lymphatic channels. The lumbar lymph glands became

stained later and to a lesser degree. By introducing a suspension of lamp black in 0.9 per cent salt solution and controlling the respiratory movements by bleeding or asphyxia, it was noted that the rate of passage of the particulate matter into the thoracic lymphatics was proportional to the violence of respiration, the absorption being purely mechanical and commencing at once. Sarcina and staphylococci passed through the diaphragm in smaller quantity than the lamp black but were scattered uniformly about the periphery of the lymph glands in fair numbers. The author concludes, in part, from his investigations that "the peritoneal cavity is drained principally by the diaphragmatic lymphatics into the mediastinal lymphatics passing through the sternal and anterior mediastinal lymphatic glands to the right lymphatic duct, and also through anastomoses in the chest to the thoracic duct. It is drained also by the diaphragmatic lymphatics into the cisterna chyli, but this path is quite subsidiary to the former. It is probably also drained to a small extent very slowly by the retroperitoneal lymphatics into the cisterna chyli."

Diphtheria Carriers among Massachusetts School Children.—BECKLER, GILLETTE and PARKER (*Jour. Infect. Dis.*, 1921, **29**, 577) found only forty-one (0.49 per cent) positive cultures of diphtheria bacilli in the nares and throats of 8389 five- to fifteen-year-old school children residing in thirty-five cities in Massachusetts. The cultures were planted on Loeffler's blood serum (Ph 7.2), and after fourteen to eighteen hours' incubation at 34° C. smears were stained with Loeffler's methylene blue and examined by the same bacteriologists. The highest percentage of positives in any one group was 13, when four positives were encountered in thirty-one cultures from one school room. Of the thirty-eight cultures on which virulence tests were conducted, all but two (95 per cent) were virulent, killing unprotected guinea-pigs in from forty-eight to sixty hours. Many diphtheroid bacilli were encountered during the examinations. In 1915 the same investigators obtained positive cultures in only 0.6 per cent of over 6000 contacts.

Presence of Bacillus Lactimorbi in the Throats of Cats.—Having shown previously that Bacillus lactimorbi occurs in the human throat, and indicated the danger of its confusion with Bacillus diphtheriæ and having also indicated the danger of its confusion with Bacillus diphtheriæ, PERKINS and SHEN (*Jour. Infect. Dis.*, 1922, **30**, 505) examined cultures from the throats of twenty-two cats in view of the recent reports inferring that these animals may be carriers of diphtheria bacilli. Swabs were taken from the noses and throats, planted on blood serum, incubated for eighteen hours at 37° C. and stained for granules. All apparently positive cultures were then heated in suspension for ten minutes at 80° C. and inoculated on glycerol agar. By this method the non-sporeforming organisms were killed. In examining smears from the second (glycerol agar) cultures, Bacillus lactimorbi was found in two out of the twelve cats in the first series and in five out of the ten in the second series. The authors again emphasize the danger of confusing Bacillus lactimorbi with Bacillus diphtheriæ and hope that their results will stimulate investigators in other parts of the country to ascertain whether this group of bacteria is common to all the states.

Is Cancer Mortality Increasing.—"To determine whether or not there is a real increase in cancer mortality we must compare cancer death rates for the same ages, since cancer is an old-age disease." Accordingly STRONG (*Jour. Cancer Research*, 1921, **6**, 251) quotes some statistics as compiled from the records of several large insurance companies. The experience of two of these companies covering the eleven-year period from 1911 to 1921 inclusive indicates, taking the figures at their face value, that for ages below sixty-five there is either a fluctuating or a slightly decreasing in cancer mortality, while for the ages sixty-five and over there is probably on the whole some increase. Meanwhile the statistics of the United States Registration Area show a continuous increase in cancer deaths. These are population statistics, however, and are not analyzed as to ages. As these deductions are from statistics one should not forget, before accepting them as final results, that certain circumstances and considerations might modify them. Certainly there has been a gradual increase in correctness of diagnosis, so that in the past many deaths attributed to old age and other diseases should properly have been ascribed to cancer, with the result that if there were a really stationary cancer mortality it would appear to be increasing considerably. The author believes "that we cannot now determine whether the cancer mortality is slightly increasing, practically stationary or slightly decreasing, but that we can be sure it is not greatly increasing." He also says "that such a conclusion does not lessen at all the seriousness of the cancer problem."

Studies on the Formol and Wassermann Reactions.—ARMANGUÉ and GONZALES (*Jour. Infect. Dis.*, 1922, **30**, 443) have been able to confirm the findings of Pauzot and of Ecker as differing from the results obtained when formol was added to sera according to the method described by Gaté and Papacostas. The technic as applied by these authors differed from the original only in that readings were made after a lapse of forty to forty-eight hours instead of twenty-four to thirty hours. Of 41 cases which were strongly positive by the Wassermann reaction only 11 were positive by formol, 4 were doubtful and 26 were negative. Just 1 was positive, 1 doubtful and 4 negative by formol in six instances where the Wassermann was weakly positive. In 127 cases where the Wassermann was negative, 5 showed positive, 1 doubtful and 121 negative by the formol method. On the other hand positive formol reactions were obtained in 67 per cent of cases of malignant tumors which yielded negative Wassermann reactions, a higher percentage than among the syphilitic patients. The sera of pregnant women (seven to nine months) always gave a negative formol reaction. Sera of dogs, rabbits, guinea-pigs, hogs, etc., were uniformly negative, but positive tests occurred in tenia infestations of dogs, in rabbits with coccidiosis and in a rabbit with hydatid cysts. It was found that formol positive serums were rendered negative by dilution with water to more than 1 to 5 and $\frac{1}{4}$1 to 6. The authors conclude "that the formol reaction was not due to some specific substance but to a relative increase of the usual constituents of normal serum, possibly globulins."

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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The Behavior of Cultures of Chick Embryo Tissue Containing Avian Tubercle Bacilli.—SMITH, WILLIS and LEWIS (*Am. Rev. Tuberc.*, 1922, **6**, 21) state that tissue cultures afford a means by which the behavior of living cells toward living tubercle bacilli can be followed under experimental conditions which are not greatly injurious to either form. Such observations have shown that: (1) Tubercle bacilli were taken in by clasmatocytes, fibroblasts, white blood cells, endothelial cells, mesothelial cells, ectodermal cells, liver cells, kidney tubule cells, and cells lining the bronchioles and alveoli of the lungs. No microörganisms were observed in red blood cells, striated muscle cells, nerve cells or ciliated epithelial cells. (2) The phenomena accompanying the appearance of tubercle bacilli within these cells were precisely the same as those shown by similar cells in regard to other foreign bodies. Entrance into cells was dependent upon the consistency of the cytoplasm of the cell, the composition of the foreign body, and also the position of the foreign body in relation to the surface of the cell. (3) Contrary to the generally accepted idea, the cell did not make any active movements toward the bacillus, nor was any migration of bacilli toward the cell observed. (4) The number of microörganisms taken in by the cell and the rapidity of the process varied greatly with the different types of cells. The clasmatocytes were the most active; after that, the giant cell, the non-granular white blood cell, the granular white blood cell, and the fibroblast, in the order named. (5) Once inside the cell, the bacilli were moved back and forth in the cytoplasm in a manner characteristic of included foreign bodies. In course of time a small vacuole formed about the microörganism, which was eventually destroyed. (6) The presence of tubercle bacilli within the cell or in the explant did not stimulate the formation of giant cells. The emulsion injected into the peritoneum of pigeons produced progressive disease of moderate severity.

Experimental Studies on the Etiology of Typhus Fever.—OLITSKY (*Jour. Exp. Med.*, 1922, **25**, 121) presents experiments to show that the typhus virus in the tissues of the guinea-pig during the height of reaction to the experimental disease does not lose its infecting power when the cells of the brain or of the spleen are disintegrated by repeated freezing and thawing, or by freezing and desiccating, or by crushing by mechani-

cal means, or by grinding into a homogeneous pulp with sand. He states that the virus after such treatment is as actively infective as in the same tissue not subjected to the disintegrating influences. The possibility exists, therefore, of an extracellular condition of the typhus virus. Fourteen attempts to filter through Berkefeld V and N candles the virus contained in the disintegrated tissue have all resulted in failure.

The Bacteriology of the Blood of Dogs with Eck Fistula.—As "there is an impression, supported by considerable evidence, that organisms from the bowel often enter the portal stream and in the liver are effectively disposed of," DAVIS and MATHEWS (*Jour. Infect. Dis.*, 1921, **29**, 313) conceived the idea that proper conditions to test this point might be furnished by Eck fistula—that is, an artificial communication between the portal vein and vena cava with the portal vein ligated above the anastomosis just at the hilus of the liver. The experiments were performed on Eck fistula dogs and consisted in taking blood cultures at varying intervals after the operation, as well as after the introduction of Bacillus pyocyaneus and Bacillus subtilis into the stomach and Staphylococcus albus into the venous circulation. All experiments were controlled by similar observations on normal dogs. It was found that in dogs with Eck fistula, bacteria do not appear in the circulation in any appreciable numbers; that Eck fistula dogs are no more susceptible to infection of lungs or of the other organs than are normal dogs and that microörganisms disappear from the circulation as rapidly in dogs with Eck fistula as in normal dogs.

Experimental Streptococcus Pneumonia and Empyema, III.—Having previously produced experimental Streptococcus empyema in rabbits by direct injection into the pleural cavity of very small amounts of a passage strain of Streptococcus pyogenes, GAY and RHODES (*Jour. Infect. Dis.*, 1921, **29**, 217) have repeated, experimentally, what is presumably the entire life history of this form of infection in man and have been able to furnish light on its exact course. By means of a soft rubber catheter pushed down the trachea amounts of culture varying from 0.01 up to 10 cc were insufflated into the bronchi of 18 rabbits. All developed bronchopneumonia followed by empyema. It was found necessary to force a small volume of air into the lungs after the streptococcus culture had been introduced into the trachea through the catheter. Similarly, pneumococcus (Type I) cultures were injected intrabronchially into a small series of rabbits. The microscopical findings in the involved areas were quite distinct from the lesions produced by the streptococcus. Death was due to a septicemia which was only irregularly encountered in the streptococcus infections. In the streptococcus infections the pneumonia is lobular in distribution, necrotizing in effect, does not resolve readily and is characterized by peribronchial and perivascular edema and later infiltration of mononuclear cells, being different from the pneumonia produced by the pneumococcus. In the streptococcus infection, pleurisy with effusion occurred, involving by extension both pleural cavities and the pericardium. It was found that the natural route of infection with the streptococcus seems to be from alveoli to pleura, rather than by the

lymphatics of the larger bronchi. Inasmuch as when injections are made into the pleural cavity the bacteria never penetrate through the pleura into the pulmonary tissue, the authors believe this would militate against the idea of a lymphatic stream from pleura to hilum. Experiments with an artificial respiration chamber seemed to indicate that the streptococcus passed from the lungs to the surface of pleura in a few minutes. The authors state that "it is evident, however, that conclusions derived from such experiments cannot explain conditions in the living body where it is found that involvement of the pleura takes place in a matter of hours (six to twelve) rather than minutes."

Negri Bodies in the Salivary Glands and Other Organs in Rabies.—JACKSON (*Jour. Infect. Dis.*, 1921, **29**, 291) examined the salivary glands from 18 rabid dogs and, as controls, from 15 normal dogs. It was found that fixation in Zenker's fluid and staining paraffine sections with alcoholic eosin and methylene blue gave the most satisfactory results. After a careful study, the author concludes that the salivary glands offer favorable conditions for the growth of certain protozoa, some of the developmental forms of which render differentiation between them and certain forms of Negri bodies impossible, or at least a very difficult task. It seemed certain, however, that in many cases of rabies, Negri bodies could be identified positively in the salivary glands. In one dog, sections from all the viscera were examined, Negri bodies being recognized in the brain and the adrenals, where they occurred in the cells of the medulla. Smear preparations of the saliva from rabid dogs failed to reveal the presence of Negri bodies.

Virulent Treponema Pallidum Recovered from a Stillborn Infant After Twenty-six Hours.—HAYTHORN and LACY (*Jour. Infect. Dis.*, 1921, **29**, 386) call attention to the fact that the Treponema pallidum occasionally retains its virulence for some hours after the death of the host—a fact which is not generally recognized and they believe a new observation. They were able to recover pathogenic, motile treponema from a stillborn infant twenty-six hours after its delivery. Great numbers of the treponema were seen by dark field illumination in the serum from superficial skin blebs and from crushed lung tissue. Rabbits which were inoculated intratesticularly with the material developed the typical lesions of experimental syphilis. The authors feel that the well preserved state of the fetus went far to explain the retained virulence of the treponemas which it harbored and stress the fact that the chance of accidental infection from careless handling of syphilitic tissue is not as remote as is generally supposed.

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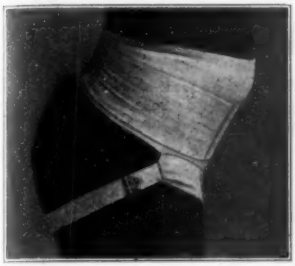

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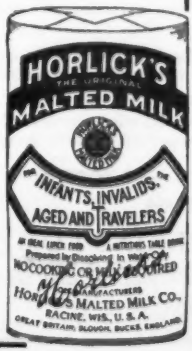

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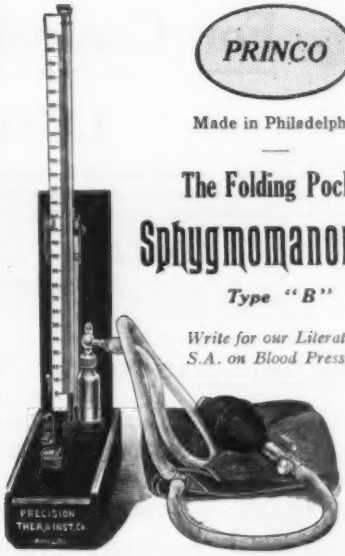

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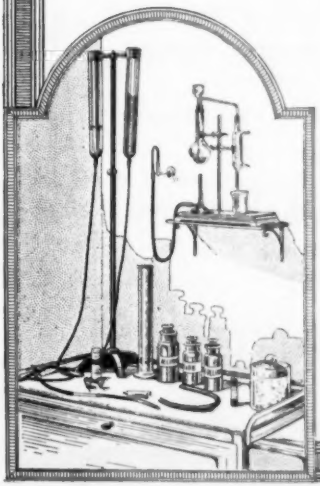

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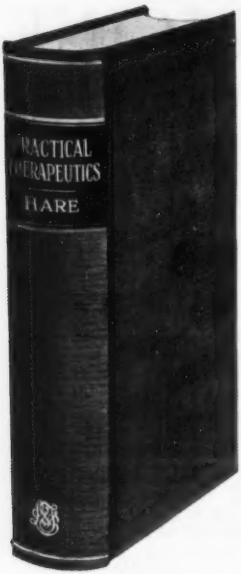

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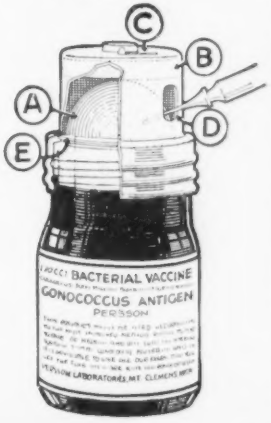

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